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A.M.A. ARCHIVES OF

INTERNAL MEDICINE

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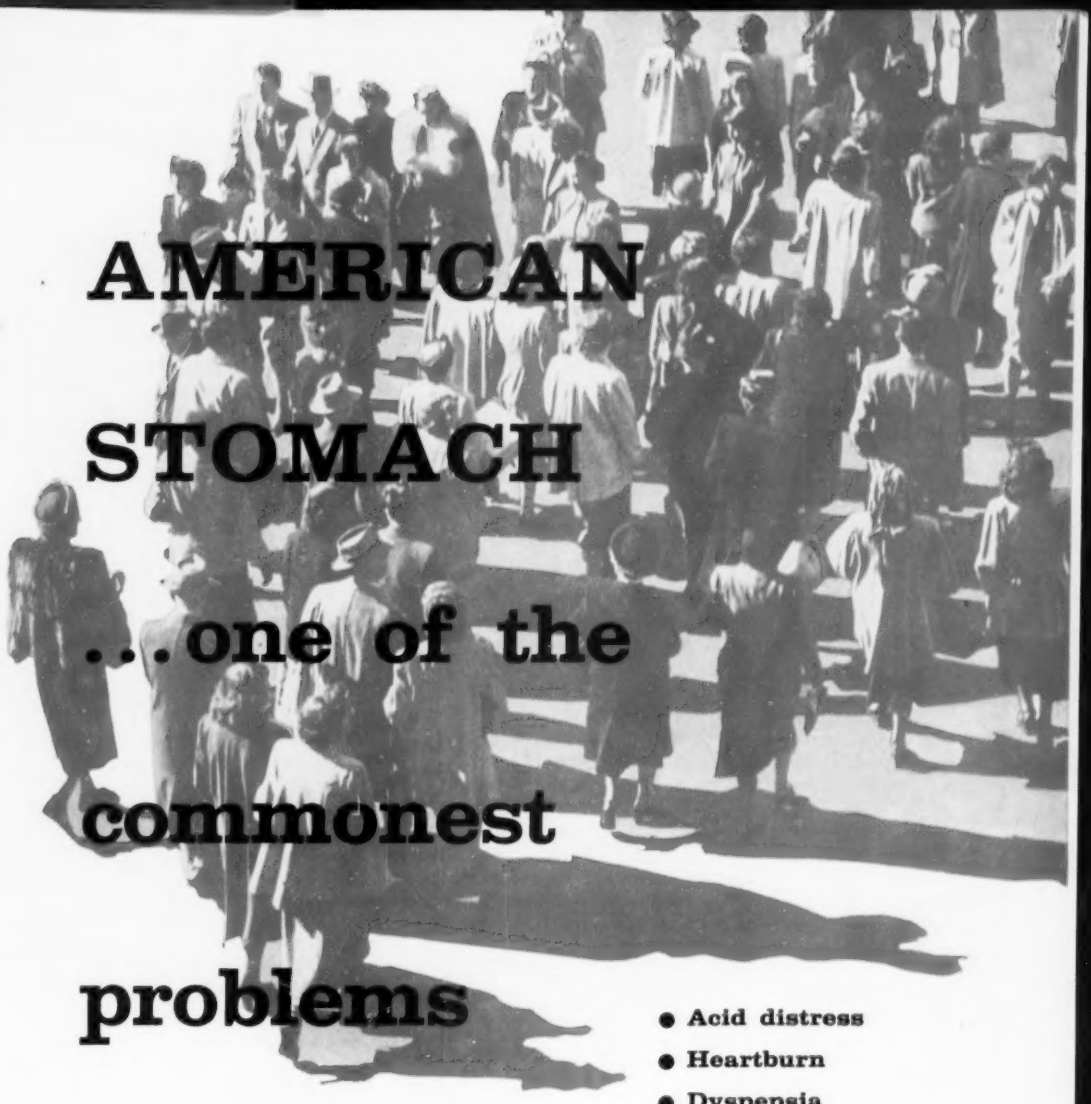

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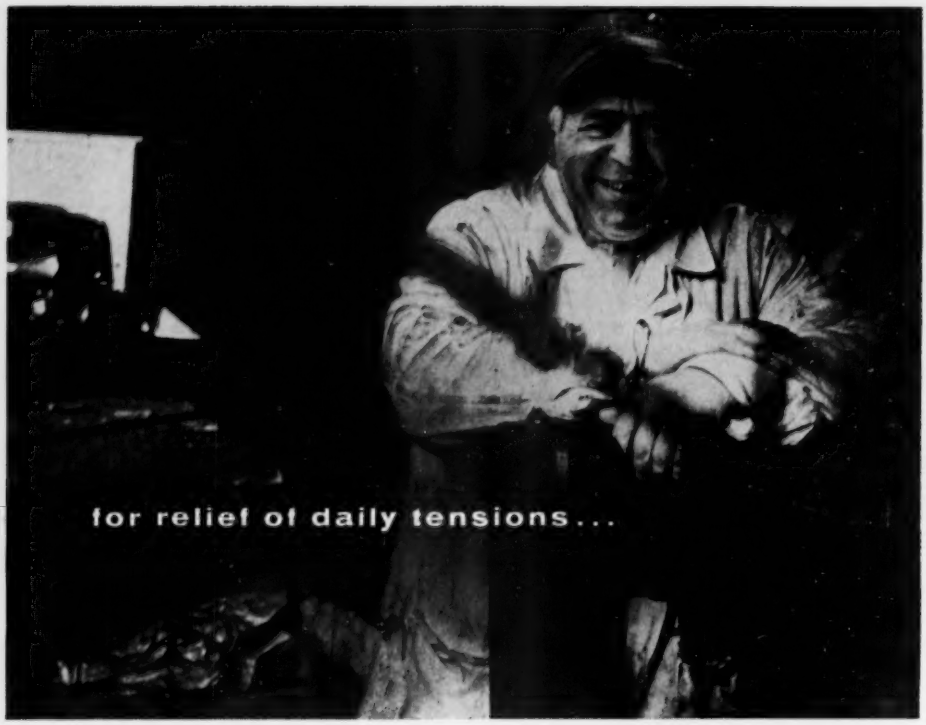

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Feeding tests with small animals and human subjects indicate the amino acids of rolled oats to be readily available for absorption and utilization because of the high digestibility of oat protein.[3, 4, 5] The high nutritional value of the rolled oats-and-milk combination was proved many years ago in human feeding experiments in which the protein value was studied in terms of maintaining nitrogen equilibrium.[6] The excellent quality of the combination of proteins in the standard serving of oatmeal and milk is also evident in results of growth tests with weanling rats.[7]

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A.M.A. ARCHIVES OF
INTERNAL MEDICINE

Recent Studies Relative to the Treatment of Diabetes*

Special Reference to New Oral Antidiabetic Drugs

ROBERT H. WILLIAMS, M.D., and ELAINE D. HENLEY, M.D., Seattle

Pathogenesis of Diabetes

Elucidation of the pathogenesis of a disease prompts a rational search for the most appropriate therapy. In the majority of patients with diabetes mellitus, the pathogenesis has not been established, but significant contributory factors have been demonstrated in some instances.

Decreased Insulin Secretion.—A marked decrease in pancreatic islet tissue, whether produced by carcinomatosis, pancreatitis, extirpation, or in other ways, has been found to cause diabetes. But in the majority of patients, apparently there is insufficient morphologic abnormality to account for the development of this disorder. It could be postulated that a biochemical defect in the β-cells is associated with a decreased insulin synthesis and/or release. Such a concept deserves notation in considering the possible mechanisms of action of sulfonylureas, discussed later.

Relative Insufficiency of Insulin Secretion.—There are many conditions that are associated with the development of diabetes in which there is reason for assuming that the amount of insulin secreted is normal or even hypernormal, particularly preceding or in the early phases of the diabetes. Indeed, in a few of these patients, the amount of insulin found in the plasma [1,2] is normal or hypernormal, despite the fact that the insulin assays may err toward showing a deficiency of insulin due to the presence in the plasma of some diabetes subjects of factors which block the action of even a standard insulin solution when injected into the assay animals. Most of the assays of the pancreas have shown a subnormal quantity of insulin [3] and may indicate subnormal secretion, but this is not necessarily the situation, since in the case of the thyroid gland a decreased quantity of thyroxin may be found with either its hypersecretion or hyposecretion.

Some of the disorders contributing to diabetes are obesity, thyrotoxicosis, pregnancy, acromegaly, Cushing's disease, pheochromocytoma, infections, severe trauma, and emotional disturbances. Diabetes has been produced in animals, recently, by the repeated administration of large doses of glucagon in oil.[4] Each of the aforementioned conditions presumably requires an increased secretion of insulin, and thereby may eventually lead to exhaustion of the β-cells of the pancreas and to a decreased insulin secretion.

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* Special article.

Factors Interfering with Localization and Action of Insulin.—Insulin apparently exerts most of its action in muscle, adipose tissue, breast, and liver.[5]

Although no insulin action in the plasma has been demonstrated, the characteristics of the plasma may greatly influence the action of insulin on tissues. Indeed, at least three different antagonistic components have been described: (*a*) in the γ-globulin, (*b*) in the α-globulin, and (*c*) in the lipoprotein fraction. Increased plasma protein binding of insulin and alterations in the γ-globulin are found particularly in subjects treated with insulin for longer than three months,[6-8] but increased plasma binding of insulin has also been observed in a few diabetes patients who apparently have never received exogenous insulin. The insulin in these subjects is bound predominantly to γ-globulin [7] and has been considered to be related to an antigen-antibody reaction. In some patients, there may be so much insulin-antagonistic activity in γ-globulin [9,10] that several thousand units of insulin per day may be required. When the plasma from such patients is mixed with a standard amount of insulin and injected into animals or assayed in vitro by measuring its effect on the glucose uptake by diaphragm, only a small fraction of the amount of insulin action is observed, compared to assays using normal plasma or saline.[1,8]

There is another antagonistic factor in the plasma of some diabetics, which when added to a standard amount of insulin decreases its action. This factor is possibly the same type that is found in the plasma of alloxanized rats [11] and depancreatized cats.[12] In these animals the antagonistic action of plasma disappears following hypophysectomy. In rats, the antagonistic factor has been demonstrated in the lipoprotein fraction of plasma.[13]

In the plasma of patients in diabetic acidosis was found [14] in the α-globulin fraction a substance which markedly antagonized the action of insulin whether the latter was injected into patients or whether insulin was assayed using rat diaphragm in the presence of the plasma. This insulin-antagonistic factor disappeared from the patient's plasma several hours after heavy insulin therapy was begun.

Thus the plasma of certain diabetic patients may contain one or more of at least three different fractions that are antagonistic to insulin: (*a*) one occurring with the γ-globulin fraction, (*b*) one with the α-globulin fraction, and (*c*) one with the lipoprotein fraction. Indeed, additional insulin-antagonistic factors may be found in the plasma. At least the first of these factors would hinder the localization of insulin in the cells of muscle and other tissues where it acts. There might also be certain abnormalities in the cells affected by insulin that would interfere with its localization and/or action. Since some investigators have concluded that insulin acts on hexokinase, the status of this enzyme in diabetic patients is of interest. However, it has been found to be normal.[15] Whether there is an excessive degradation of insulin in the body tissues of diabetic patients has not been proven.[16,17]

In conclusion, it is evident that there are numerous entities — pancreas, pituitary, adrenal, thyroid, liver, immunologic responses, and other—that affect the development and course of diabetes mellitus. These must be considered in designing therapy.

Therapies for Diabetes

Insulin.—Most attention in the therapy of diabetes, during the last few decades, has been directed toward providing different types of insulin,[18] and the recent contributions by Hallas-Møller et al.[19,20] are noteworthy. By using an acetate buffer rather than the usual phosphate buffer, it was found that zinc-insulin crystals were more slowly absorbed, and, consequently, delayed action could be obtained without using an additional foreign protein, such as protamine. The duration of action is directly proportional to the size of the crystals used. A preparation designated "ultralente" has

crystals 10-20μ and acts as long as protamine zinc insulin. Another preparation, "semilente," is composed of very fine particles in an amorphous state, and its duration of action is intermediate to regular insulin and isophane (NPH) insulin. "Lente" consists of 30% semilente and 70% ultralente, and its duration of action is similar to that of isophane insulin. By using different ratios of these compounds essentially any desired duration of action can be attained. Therefore, it appears that nearly maximal progress has been made with this type of therapy.

Benefit would be derived if the pancreas could be stimulated, by an orally administered compound, to increase secretion of insulin. As discussed later, this may be one important action of sulfonylureas.

Iatrogenic Hypoadrenocorticism or Hypopituitarism. — Since somatotropin and glucosteroids exert antagonistic actions to insulin, reduction in their secretion decreases the amount of insulin required. For severe diabetic kidney disease and/or retinitis, adrenalectomy or hypophysectomy has been performed.[21,22] Whereas, the insulin requirements are markedly reduced, it is questionable as to whether the net advantages outweight the disadvantages. Recently, it has been shown [23] that a marked decrease in the urinary excretion of adrenal corticoids and in insulin requirements in diabetes could be produced by the oral administration of Amphenone B (1,2-bis-[*p*-aminophenyl]-2-methyl propanone-1). However, this compound is so toxic that it should be used rarely.

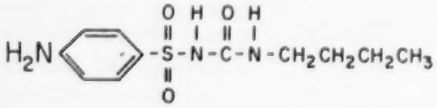
Corticoid.—In certain patients with marked resistance to insulin, supposedly on an immunologic basis, corticoid therapy may be of advantage.[24] Its beneficial effects in decreasing the production of insulin antibodies apparently outweigh its gluconeogenetic effects.

Other Compounds.—For several decades, as indicated by the reviews of Best,[4] Houssay,[25] Lewis,[26] Kuizenga,[27] Young,[28] and others, searches have been made for a compound which would be effective orally in the treatment of diabetes. Benefit has been claimed for a variety of compounds, including extracts of bacteria, molds, and yeast and of the roots, stems, leaves, and berries of certain plants. Synthetic products have also been studied. Special attention is called [28] to the hypoglycemic effects of certain guanidines, acridines, sulfonamides, and penicillin, each of which also exerts antimicrobial action. Houssay [25] investigated a large number of sulfur compounds that not only protected against alloxan diabetogenesis but also improved the diabetic state; thiouracil was one of the compounds studied. Amellin, galigen, myrtillin, lupanine, and synthalin are included. However, extension of the studies has shown them to be ineffective or toxic. In 1942 the study of a new type of compound was initiated as a result of an accidental observation of Janbon [29] that a typhoid patient experienced a hypoglycemic reaction related to therapy with *p*-aminobenzenesulfonamidoisopropylthiodiazole (IPTD). Subsequently, Loubatières [30] reported that whether this agent was administered orally or intravenously it produced hypoglycemia in many species. Other of his most pertinent observations were as follows: (*a*) IPTD increased the concentration of glycogen in the liver, (*b*) it did not cause hypoglycemia in depancreatized animals, (*c*) its administration into the pancreatic artery caused profound hypoglycemia, and (*d*) with cross circulation experiments the administration of the compound to a normal donor dog produced marked hypoglycemia in the alloxanized recipient. These and other studies led him to conclude that IPTD increases insulin and decreases glucagon secretion. Von Holt,[31] in studying the mechanism of hypoglycemia, observed damage to the α-cells, and he considered the hypoglycemia to be due to decreased glucagon production and insulin stimulation. Meanwhile, Chen [32] observed that *p*-aminobenzenesulfonamidocyclopropylthiodiazole caused hypoglycemia in intact rats and hyperglycemia in alloxanized rats.

Another study of antibacterial agents led to the discovery of carbutamide.[33] Fuchs, a resident in medicine, observed hypoglycemic manifestations soon after ingesting some of the compound. In the last two years this observation has led to extensive studies of many related compounds by numerous investigators, but most attention has been given to carbutamide and tolbutamide.

Basic Studies with Carbutamide and Tolbutamide †

Chemistry and Metabolism.—Carbutamide is the generic name for 1-butyl-3-sulfanilylurea (Fig. 1), also designated BZ-55,



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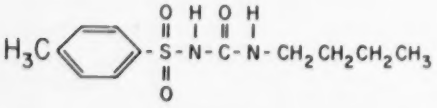

TOLBUTAMIDE

Fig. 1.—Note that tolbutamide is like carbutamide except for a methyl group instead of an amino group.

Nadisan, and Invenol. Tolbutamide is the generic name for 1-butyl-3-*p*-tolylsulfonylurea, which is also called D-860, Orinase, Rastinon, and Artosin. Tolbutamide differs structurally from carbutamide only in that it has a methyl instead of an amino radical, in the para position. Carbutamide inhibits the growth of pneumococci, streptococci, and staphylococci,[34] whereas tolbutamide has no antibacterial action. Each compound produces hypoglycemia whether administered orally or parenterally. After oral administration to man some drug is demonstrable in the blood within 30 minutes[33] and a peak concentration in 3 to 5 hours. Present evidence indicates that tolbutamide remains in the extracellular spaces, whereas part of carbutamide becomes intracellular.[35-37] Each compound is bound to plasma albumin; tolbutamide is bound tighter than carbutamide. Throughout the first two hours the concentration in the liver is only about two-thirds that of plasma.[37] In the liver cells distinctly the largest concentration is found in the supernatant fraction[37] following high-speed centrifugation of disintegrated cells. Carbutamide is excreted very slowly. Indeed, with the average therapeutic regimen four days or longer is required for complete clearance. Tolbutamide is excreted faster. The main excretory product of tolbutamide is butyl-*p*-carboxyphenylsulfonylurea,[38-41] which results merely from the oxidation of the methyl to a carboxyl group. This excretory product has no hypoglycemic action.[42] A major portion of carbutamide is excreted in an acetylated form, but relatively little carbutamide in blood is acetylated.[33,34] The transformation product of each of these sulfonylureas is readily soluble in acid urine. For example, the tolbutamide metabolite is soluble to the extent of 1 gm/100 ml. of water.

With severe acute poisoning there are ataxia, paresis, convulsions, and hyperglycemia.[34,43]

Effect on Glucose Metabolism.—Blood and Urine Sugar: In normal man given tolbutamide, Mirsky[44] found that with increase in the oral dosage from 10 mg/kilogram to 50 mg/kilogram there was an increase in the degree and persistence of hypoglycemia, but doses greater than 50 mg/kilogram did not cause further hypoglycemia. The maximal drop with all doses was found in from 30 to 60 minutes. The degree of initial hypoglycemia was the same with 50 mg/kilogram of tolbutamide orally as with insulin given intravenously, 0.1 unit/kilogram (Fig. 2), but there was a

† In this paper, as in papers by many others, the term "sulfonylurea" is used with reference only to carbutamide and/or tolbutamide. In many studies, particularly clinical ones, these two compounds have frequently been interchanged. Their actions, including potency, are very similar; significant differences are mentioned in appropriate places.

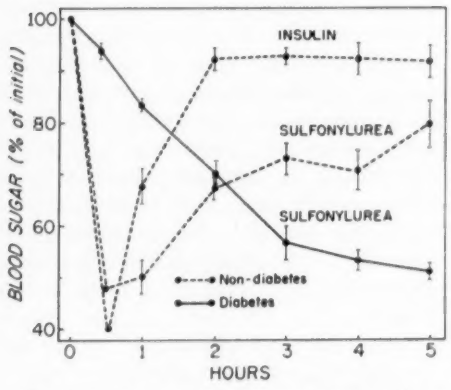

Fig. 2.—When tolbutamide was given orally to fasting nondiabetic subjects, 50 mg/kilogram, a rapid drop in the blood sugar occurred, comparable to that following insulin administered intravenously, 0.1 unit/kilogram. However, after tolbutamide, there was a much slower return to normal. The fall in blood sugar, produced by sulfonylurea, in subjects with diabetes was much slower than in those without this disease. Replotted from charts by Mirsky.[44]

much slower return of the blood to normal in the subjects given tolbutamide. The fall in blood sugar in diabetes patients was much slower than in normals (Fig. 2). As shown in Figure 3, the repeated administration of tolbutamide to responsive diabetic persons maintained the blood sugar at a lower level than when no treatment was given. Indeed, in some subjects the level was lower than with two daily doses of insulin, but the profile throughout the day was similar in each instance. This is of extra interest, since it has been shown that under certain conditions carbutamide decreased the rate of absorption of glucose from the gastrointestinal tract.[46] In animals, huge doses of sulfonylurea have been found to cause hyperglycemia rather than hypoglycemia.[34]

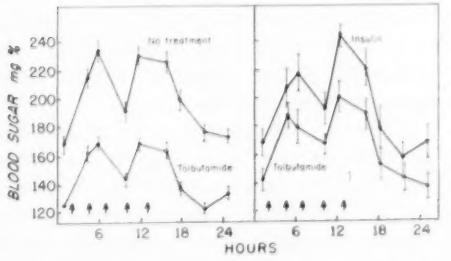

Fig. 3.—As shown in the plot on the left, the daily blood sugar profile in 100 diabetes patients responsive to sulfonylurea was lower but similar to the pretreatment pattern. In 15 subjects, as shown in the right plot, the average daily blood sugar values was lower than with two daily doses of insulin (16 plus 8 units as the average). Replotted from charts by Mohnike and Stötter.[45]

Ordinarily the glycosuria decreases in proportion to the decrease in blood sugar.

Liver: In analyzing the mechanism of production of hypoglycemia, evaluation of the amount of hepatic glycogen synthesis, glucose oxidation, and glucose release is very important. Whereas sulfonylurea therapy did not cause hypoglycemia in eviscerated animals,[35,47] it did cause it in hepatectomized ones.[47,48] Nevertheless, the sulfonylureas have caused many different alterations in chemical reactions in the liver. Although there are reasons[49] for concluding that glycogenesis is not impaired in tolbutamide-treated normal rats, there are evidences that glycogenolysis may be inhibited. In fasting animals the drug was associated with less depletion of liver glycogen,[36,49,50] which resulted, at least partially, from a decreased release of glucose from the liver. Indeed, a few minutes after the intravenous administration of sulfonylurea a marked decrease in the glucose concentration in the hepatic vein was observed.[51] Moreover, the glucose output from liver slices of tolbutamide-treated rabbits was decreased.[49] Addition of the compound in vitro did not affect the glucose output,[49,52,53] although some investigators have reported inhibition.[54,55] One explanation for the decreased glucose output is the inhibition of glucose-6-phosphatase, demonstrated by several investigators.[49,56,57] In this regard, the question may be raised as to whether the effects are primary or secondary to an increased secretion of insulin (*a*) since tolbutamide did not inhibit glucose output in vitro,[49,53] (*b*) since no change in glucose-6-phosphatase activity was demonstrated in the liver of alloxanized animals,[37,58] (*c*) since insulin decreases this enzyme, and (*d*) since, as discussed subse-

quently, sulfonylureas may increase insulin production. That there must be factors additional to glucose-6-phosphatase inhibition is suggested by the observations that several hours are required for the insulin effect on this enzyme [59] and more than 2 hours for tolbutamide,[37] although hypoglycemia can be demonstrated in 30 minutes. Moreover, tolbutamide, unlike insulin, decreased the total amount of glucose-6-phosphatase action in liver.[60] There is some evidence to suggest that the sulfonylureas may inhibit phosphoglucomutase [27] and activation of phosphorylase.[60]

The inhibition of glycogenolysis by sulfonylureas can be overridden by epinephrine or glucagon. The response to glucagon has been found different by various investigators, doubtless due to differing doses and other conditions. Some have found a normal hyperglycemic response to glucagon,[42, 61,62] while others have found a decrease [63,64] or an increase.[65] Likewise, with in vitro studies some have reported normal responses [49,60,66] and others a decrease.[53] Interestingly, Anderson [65] has found that diabetes patients who have a marked hyperglycemic response to glucagon do not respond well to sulfonylureas and vice versa.

The hyperglycemic response to epinephrine was found the same with and without tolbutamide.[61,62] With in vitro studies some investigators found inhibition of glucose output,[53,55] while others found none.[66]

After carbutamide, infusions of fructose or of galactose did not cause the usual increase in blood glucose.[67]

One hour after tolbutamide administration Fajans [42] found the blood pyruvate decreased, whereas at the same interval following insulin it was increased. Moorhouse [68] found a depression of pyruvate and lactate. Steigerwald [69] also found a decrease in lactate but an increase in pyruvate.

Muscle: Sulfonylureas have been found in vitro not to increase the glycogen of muscle,[36,49,50,59,66] in either the presence or absence of insulin. Under certain conditions they did not increase the A-V glucose difference [63,70] or increase glucose utilization.[67] However, since they decrease glycosuria and hyperglycemia and do not appear to influence gluconeogenesis, they must indirectly increase glucose utilization. Indeed, using glucose-C^{14} it has been found that tolbutamide increased glucose oxidation in normal rats but not in alloxanized animals [71] and not in nephrectomized eviscerated rabbits,[35] indicating again the necessary presence of the pancreas for action of the drug.

Numerous investigators have found that the sulfonylureas commonly cause a lowering of the hyperglycemia in glucose tolerance tests but do not affect the pattern.[42,62,67] The insulin tolerance test remains unchanged. Moreover, the insulin requirements in most juvenile diabetes patients are not reduced, indicating that with the usual therapeutic regimen the sulfonylureas do not significantly increase the effectiveness of insulin.

Adipose Tissue: The sulfonylureas have been found not to increase the glucose uptake by adipose tissue or to increase the effectiveness of insulin.[72]

Effect on Hormones Affecting Carbohydrate Metabolism. — Insulin and Glucagon Secretion: The sulfonylureas have been found by many investigators to exert no significant hypoglycemic effect in depancreatized patients [62,70,73] and animals [34,47,74] or alloxanized rats.[34,36,75] Although responses to these drugs have been observed in depancreatized subjects [76-78] and commonly in mildly alloxanized animals, it is probable that in these instances some activity by pancreatic islets must remain.

Following the administration of carbutamide to rats for several weeks there was found an absolute increase in the weight of islet tissue.[79] It was also increased significantly relative to the total body weight and the total pancreas weight.

Although there have been many specific searches for anatomical damages of the α-cells, produced by tolbutamide or carbutamide, none has been found, except occasionally in animals when enormous doses have

been administered. In six patients subjected to autopsy no alterations were found.[80]

The changes in the β-cells have consisted chiefly of changes in granularity and hydropic alterations, but these histological changes are inadequate for indicating an increase in secretory activity. Actual insulin assays of the pancreas in dogs treated with carbutamide for eight weeks have been normal, but two days after the administration of large doses there is a marked decrease in pancreas insulin.[81] Colwell found,[82] after infusing 7 mg/kilogram of carbutamide over an interval of 20 minutes into the right gastroepiploic artery of dogs, that hypoglycemia was produced, whereas the same amount of drug infused in the femoral vein was without effect. No changes were found in the α- or β-cells or in the insulin content of the pancreas. The observations are in keeping with those of others,[30,83,84] and possibly suggest that an increased production of insulin results. Pancreatic insulin assays demonstrate that the types of diabetes patients who respond best to sulfonylurea therapy tend to have the most insulin in the pancreas.[85]

After sulfonylurea therapy the quantity of glucagon-like activity in the pancreas [60] and blood [86] have been found normal, but the assays, particularly of blood, are unsatisfactory.

Insulin Metabolism: In relatively high concentrations tolbutamide and carbutamide inhibit degradation of insulin in vitro,[87,88] exerting a noncompetitive type of inhibition. However, with the ordinary clinical doses of the compounds there is evidence that this action plays relatively little role in producing hypoglycemia.[88] Further support of this conclusion is given by the following observations, previously discussed: (*a*) the failure of the sulfonylureas to reduce significantly the insulin requirements in totally depancreatized subjects, or in the majority of patients with juvenile diabetes, and (*b*) the failure to alter the insulin tolerance test. The distribution and degradation of insulin-I^{131} in tolbutamide-treated intact rats were normal,[48] although under a different set of experimental conditions a decrease in degradation in intact mice was reported.[44]

Most patients treated with insulin for more than a few months have been shown to have an increased plasma-protein binding of insulin,[7,8] but approximately one-half of those who have a satisfactory response to tolbutamide showed a reduction in this binding capacity.[62]

Adrenal: Adrenalectomized animals have a more marked hypoglycemic response to sulfonylureas than any other group.[36,47,48] Moreover, the hyperglycemic response found after administering large doses to intact animals was found not to occur in adrenalectomized animals.[89] Adrenal demedullated animals [90] also have a hypernormal hypoglycemic response, but it is not as great as that following total adrenalectomy.

Prolonged administration of the sulfonylureas has been reported to be unassociated with adrenal changes.[33,48] Moreover, these drugs have not altered the urinary excretion of 17-ketosteroids or 17-hydroxysteroids [42,64,91] and have not changed the sodium, potassium, or nitrogen balance.[42] Prednisolone caused the same organic and inorganic changes in man with sulfonylurea therapy as without it.[42] Also, diabetes produced by cortisone or prednisone was not influenced significantly by tolbutamide therapy.[92] On the other hand, diabetes associated with Cushing's disease may show significant benefit.[45]

Pituitary: No significant anatomical changes in the pituitary have been reported following sulfonylurea therapy. Hypophysectomized cats,[74] rats,[48] and patients [42] have been found to respond with the same degree of hypoglycemia as normals. Since such animals have a marked decrease of adrenal function as well as an absence of pituitary function, it is surprising that they do not have a hypernormal response. These observations, added to Young's [28] showing that a cat with metahypophyseal diabetes was cured with carbutamide, raise the question as to whether some of the antidiabetic effect of the sulfonylureas might be related

to an action on the pituitary or in association with one of its hormones, particularly somatotropin.

Hypophysectomized cats that are also depancreatized were found to have no hypoglycemic response to sulfonylurea.[74]

Thyroid: Prolonged therapy with large doses of carbutamide produce thyroid acinar hyperplasia and goiter.[34,93] This was to be anticipated since many *p*-aminobenzenesulfonamides have been known to produce such changes. In many clinical studies[94] carbutamide, after one dose, has been found to inhibit I^{131} uptake by the thyroid, whereas tolbutamide had only very slight effect. After using either compound for several weeks, at the average dosage, there was not a very significant effect on I^{131} uptake, protein-bound iodine of the plasma, or basal metabolic rate. Moreover, myxedema has not resulted.

Effect on Lipid Metabolism.—In diabetes patients, who for several weeks have shown a good response to tolbutamide, there has been found[95] a decrease in blood cholesterol and total lipids, but a slight increase in the phosphatides. Carbutamide has been reported to decrease hyperketonemia in papatients given an unusual diet high it fat, leading to a suggestion that the primary effect of the drug might be upon fat oxidation.[96] However, there is no significant effect on the ketonemia of diabetic acidosis.

Carbutamide and Tolbutamide Therapy in Diabetes

Although the first public announcement of the usefulness of carbutamide in the treatment of diabetes was made only about one year ago,[33,34,97] the literature on this drug and on tolbutamide has become voluminous.[62,76,94,98-118] Many of the reports are based upon relatively small series of patients. The largest series (781 patients) is included in a cooperative study reported by Mohnike and Stötter.[45]

The material presented here is based chiefly on (*a*) a digest of the literature, (*b*) information obtained at various symposia and conferences, including European representatives as well as American, and (*c*) experiences of our own in the treatment of 129 patients.

There is reasonably good agreement relative to the types of responses in diabetes patients, but there are differences in opinion relative to untoward effects, probably because large series are required for appropriate evaluation of this phase.

Responses in Diabetes and Factors Influencing Them.—Essentially all gradations of response may be obtained with different

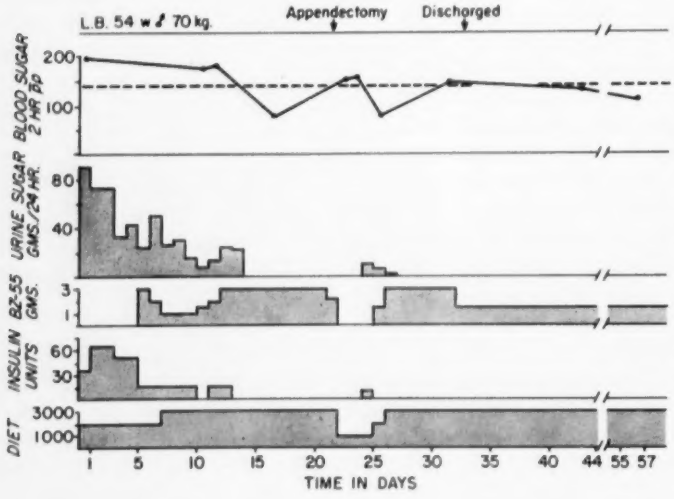

Fig. 4.—Note that glycosuria disappeared and the hyperglycemia decreased with carbutamide, despite cessation of insulin treatment. Appendectomy caused only slight disturbance in the carbohydrate status. Reproduced with permission from Cox, R. W.; Henley, E. D.; Fergus, E. B., and Williams, R. H.: *Diabetes* 5:358-365, 1956.

patients with diabetes, varying from no response (or even hyperglycemia) to very satisfactory control of the disease—sometimes even better than with insulin (Figs. 3 and 4). It may be estimated that approximately 50% of all diabetes patients show a reasonably satisfactory response to carbutamide or tolbutamide. This response is essentially the same with the two drugs. In our own series of 129 patients satisfactory results have been obtained in 91. In order to be labeled "satisfactory" there should be (*a*) a significant drop in the blood sugar, with two-hour postprandial specimens containing less than about 160 mg. per 100 cc., (*b*) less than 0.25% sugar in essentially all urine specimens, (*c*) control of diabetes symptoms, and (*d*) no untoward reactions, other than mild transient ones.

Since, upon substituting sulfonylurea therapy for insulin, some of the patients who do not respond satisfactorily may develop severe acidosis, or other difficulties, it is important to select patients who most likely will respond satisfactorily. Appropriate predictions can be made in almost 90% of the patients, when their characteristics are correlated with previous responses of similar subjects to this oral drug therapy and when a "screen test," described subsequently, is performed. Some of these characteristics are now discussed.

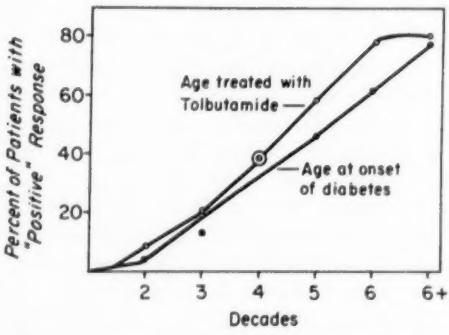

Fig. 5.—The age of the patient at the onset of his disease or at the initiation of tolbutamide treatment and the percentage of patients responding to therapy correlate better than any other characteristics. Reproduced with permission from Mohnike, G., and Stötter, G.: *Deutsche med. Wchnschr.* 81:826-835, 1956.

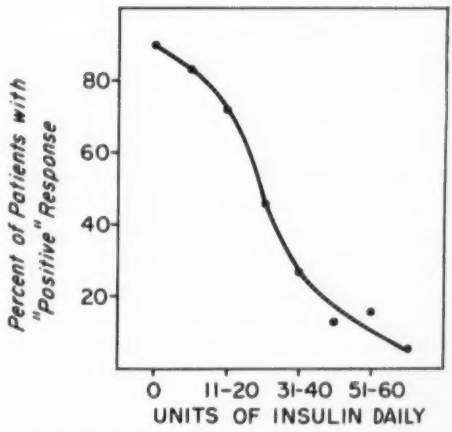

Fig. 6.—The smaller the dosage of insulin required to control the diabetes the greater percentage chance is there that the patient will respond to tolbutamide treatment. Reproduced with permission from Mohnike, G., and Stötter, G.: *Deutsche med. Wchnschr.* 81:826-835, 1956.

As shown in Figure 5, the age of the patient is highly important in prognosticating the response. The age of the patient at the time of onset of diabetes and also his age at the time that sulfonylurea therapy is instituted are very important. Very few subjects below 20 years of age respond, whereas 80% of those over 60 have a favorable response.

Another important correlation is the previously required insulin dosage and the percentage of patients responding to sulfonylurea therapy (Fig. 6). The larger the amount of insulin that has been required the less are the chances that the patient will respond satisfactorily to oral therapy. There also is a relatively good correlation between the amount of insulin found in the pancreas by Wrenshall [85] and the responsiveness to drug therapy.

Other factors that are considered by some investigators (denied by others) as favorable to a good response are obesity, a stable type of diabetes, recent onset of the diabetes, and little or no previous insulin treatment. Several patients with Cushing's disease have had gratifying results, whereas essentially no response was obtained from iatrogenic steroid diabetes. Diabetes with

hypertension responds fairly well, and much better than that with retinopathy [45] as the only complication. In our experience, patients with pronounced complications usually responded poorly.

Depancreatized patients apparently do not respond if all pancreas has been removed. Other factors that are reported to be unfavorable [45] are leanness, thyrotoxicosis, hyperactive autonomic nervous system, unstable type of diabetes, ketosis, severe infection, or other stressful situations.

Untoward Reactions to Sulfonylurea Therapy.—Because of previous experiences with untoward reactions to sulfonamides, many of which were serious, there has been a special search for similar reactions to carbutamide and tolbutamide. Many tissues known to be subject to sulfonamide sensitivity—skin, bone marrow, liver, and kidneys—have been under careful observation. However, relatively few reactions have been reported from Germany and, until recently, few in the United States. Recently a survey by Kirtley [118] of 7193 patients treated with carbutamide revealed that 389 (5.36%) had experienced untoward reactions (Table 1). Rashes constitute the commonest reaction and may consist of urticaria, exfoliative dermatitis, or a morbilliform or other type rash. Anorexia, nausea, and vomiting are not uncommon but usually are transient.

TABLE 1.—*Reactions in Carbutamide-Treated Patients**

	No. Cases
Rash	109
Anorexia, nausea, vomiting	81
Malaise, lethargy, fever	79
Agranulocytosis, leukopenia	58
General allergy	25
Cardiovascular, renal	16
Exfoliative dermatitis	6
Acute anemia	6
Jaundice, liver function	6
Acute edema	4
Crystalluria	3
Thrombocytopenia	2
Purpura	2
Eosinophilia	2
"Headache"	2
Psychosis	1
Hypothyroidism	1
Methemoglobinemia	1
Tachycardia	1
Sudden myocardial failure	1
Unclassified	10

Total patients 7193; reaction in 389 (5.36%)

* Reproduced with permission from Kirtley.[118]

TABLE 2.—*Untoward Reactions to Tolbutamide**

	Patients, per Cent
Dermatologic	1.0
Leucopenia†	.05
Others‡	1.2
Hepatic	0
Deaths attributed to drug	0

Total patients 2,052; reaction in 47 (2.2%)

* Data were supplied by C. J. O'Donovan, The Upjohn Company.
† Total white blood cell count 2,850; 28% PMN.
‡ Nausea, malaise, headache, epigastric distress, etc.

Headache, fever, malaise, and paraesthesias are complaints occasionally. Frank agranulocytosis has occurred in a few instances. Interstitial myocarditis, toxic hepatitis, acute hemolytic anemia, and the other conditions listed in Table 1 have been observed. There have been eight deaths attributed to carbutamide. Most of the untoward reactions presumably were due to hypersensitization to sulfonylureas. It is difficult to be sure that all of them were actually due to sulfonylurea therapy. Some of the patients had taken other drugs that could have been responsible. Moreover, it is important to recall that diabetes patients are more apt to have other afflictions. In the fifth decade death is three times as common in diabetics as nondiabetics. Root reported [111] that in 279 patients treated with carbutamide 33 untoward reactions developed in 26 patients, an incidence of 9.2%. These consisted of skin rash in 15, jaundice in 4, nausea and vomiting in 4, diarrhea in 2, hypoglycemia in 2, paroxysmal auricular tachycardia in 1, acute anemia in 1, and disorientation in 1. Of 16 patients treated with carbutamide for six to nine months, all had an increase in alkaline phosphatase, but normal results were obtained with the following tests: sulfobromophthalein (Bromsulphalein), thymol turbidity, and van den Bergh.

In a few instances hypoglycemia has been severe, but it tends to be less frequent and severe than with insulin treatment.

As seen in Table 2, the untoward reactions to tolbutamide have been somewhat similar but much less frequent, and they also are less serious.

We have given 146 courses of sulfonylurea therapy to 129 patients as follows:

94, tolbutamide alone; 18, carbutamide alone, and 17, carbutamide followed by tolbutamide. While tolbutamide was given there were five patients with nausea, two with paraesthesia, and two with weakness (probably hypoglycemia reaction). Among those receiving carbutamide there were five with nausea, two with giddiness, and one with paraesthesia. All of the reactions were mild and transient.

It is of interest that no severe kidney disturbances have been reported. Because the sulfonylurea metabolic products have a high degree of solubility, crystalluria has not been a problem. Whereas a sulfonamide nephritis has been established as an entity, it has not been reported to occur with sulfonylureas. A false-positive albuminuria test may be obtained with sulfosalicylic acid and other such acidic agents and results from precipitation of the drug excretory product.

Short Test for Sulfonylurea Responsiveness. — Consideration of the factors, discussed earlier, influencing the response to sulfonylurea therapy helps greatly in selecting the patients for this treatment. In general, the older the patient and the smaller his insulin requirements the better will be his results. Since one cannot predict the results with certainty and because change from insulin therapy to sulfonylurea treatment and vice versa requires psychological as well as metabolic readjustments, any measure which would help select the responsive patients would be advantageous. For this purpose short screening tests have been developed.[44,164,111,113-116] A convenient and satisfactory procedure is as follows:

1. Use short-acting insulin instead of long-acting for two days before the test.
2. On day of test no food or insulin is given, until completion of the test.
3. Three grams of carbutamide or tolbutamide is given orally, as a single dose.
4. Blood for sugar determinations is drawn at zero and four hours (two-hour and six-hour specimens may also be taken). Normal subjects usually have more than 20% drop in blood sugar at four hours. Ordinarily, patients with maturity-onset diabetes have more than a 30% drop (Fig. 2), while those with juvenile diabetes usually have no drop; indeed, in the latter there may be a rise. A few patients who have a significant drop in blood sugar with this acute test do not respond satisfactorily to sulfonylurea therapy and vice versa. In approximately 90% of those with a positive acute test there is a response to continued sulfonylurea therapy.[111]

The difference in the pattern of fall in diabetes and in normal subjects has been used for the early diagnosis of diabetes.[113]

Treatment Regimen Used by Us.—So few patients with juvenile diabetes respond that we rarely attempt sulfonylurea therapy in this group. Before its use is contemplated in any patient with severe diabetes he should be subjected to the short test for sulfonylurea responsiveness, because in some of the patients in whom this type of treatment is ineffective a severe diabetic acidosis may develop.

Despite the fact that untoward reactions to sulfonylureas have not been proven to occur more frequently in certain patients than others, experiences with other drugs make it seem wise to use sulfonylureas much more hesitantly in patients (*a*) who have previously exhibited hypersensitivity reactions, particularly to sulfonamides, (*b*) who have a collagen disease, or (*c*) who have liver disease or certain hemocytological disorders.

The subjects selected for therapy are given tolbutamide,‡ 1 gm. three times daily on the first day, 1 gm. twice daily on the second day, and 0.5 gm. twice daily thereafter. In some instances when there has been little or no response in one week the daily dosage is increased to 2 or 3 gm. for an interval of approximately one week. Although most of the patients who are going to respond do so within the first week,

‡At present we prefer tolbutamide to carbutamide because there have been fewer side-reactions. However, additional studies are required to determine more accurately the incidence and nature of the reactions to tolbutamide.

a few require two weeks. When there is little or no response to the increased dosage this type of therapy is abandoned. In those given continuation of treatment the dosage is reduced to 1.0 gm. or less (usually 1 gm.) per day, given in two doses. The customary general attention is given to diet, weight reduction, and care of infections.

In most of our patients on the first day of tolbutamide therapy about one-half of the usual dose of insulin is given, but thereafter it is administered only if the tolbutamide is not controlling the diabetes. This applies particularly when infections or other stressful situations develop. Indeed, ordinarily when some severe disorder, such as lobar pneumonia, develops it is preferable to use only 0.5 gm. of tolbutamide daily and to use insulin until the crisis has passed. From the point of view of controlling the diabetes the drug could be replaced, temporarily, completely by insulin, but sensitivity reactions are presumably less likely to develop if tolbutamide is given daily. A few patients have been reported to be best controlled by using insulin plus tolbutamide indefinitely. However, this dual therapy is not desired unless the oral treatment has been demonstrated to reduce significantly the dosage of insulin required. We rarely use insulin and tolbutamide over long intervals.

The patient should be prepared for hypoglycemic reactions, even though severe ones are rare. He should consult his physician, at least by telephone, if he develops a sore throat, fever, malaise, or, indeed, any illness. The physician can then decide whether the patient needs to be examined immediately; in most of such situations he should be. With certain drugs, agranulocytosis has been found despite a normal white blood cell count two days previously. For this reason it has long been the policy of one of us (R. H. W.) to perform white blood cell counts immediately upon indication rather than to perform a large series of routine ones; the same applies to certain other examinations. However, the patient should be seen at regular intervals, at which time the physician can deal with various situations in the manner indicated. In most cases determinations of the drug level in the blood has not been of definite value.

In relatively few patients does the diabetes remain permanently under control after cessation of therapy. In this connection the studies of Mohnike and Stötter[45] are of special interest. The sulfonylurea therapy was stopped in 50 patients who had responded well. In 19 there was "metabolic decompensation" within 5 or 6 days; in 10, within 10 to 14 days, and in 21, within several weeks. Because of the almost invariable relapse and because of the presumably increased chance of developing hypersensitivity reactions with intermittent therapy it is desirable to give tolbutamide continuously.

Because, as discussed earlier, one of the main mechanisms of action is presumed to be stimulation of insulin secretion, and since prolonged excess stimulation of the β-cells has long been considered a cause of permanent diabetes, the question arises as to whether eventually the diabetes will be made worse by this type of treatment. Many years may be required to answer this satisfactorily, but present evidence in animals and patients suggests that such is not the case after several months of therapy. In most instances the amount of insulin required to control the disease is the same after sulfonylurea therapy as before; in a few subjects it is more and in a few it is less.

A View of Potential Future Therapy

Considerable research now under way may provide improvement in therapy. Better control of the insulin-antagonistic factors in the plasma, of hormones with counterinsulin effects, and of insulin degradation are all important approaches. Many compounds have been shown to inhibit the degradation of insulin in vitro,[16,44,119-121] and some of these have been reported to produce hypoglycemia. Results with the amino acids are noteworthy because they

are noncompetitive inhibitors, are natural body constituents, and may be less toxic than the sulfonylureas.

Summary and Conclusions

Searchers for improvement in the treatment of diabetes mellitus will benefit as its pathogenesis is more thoroughly elucidated. Although in certain cases (e. g., cancer of the pancreas) there is evidence for an absolute deficiency in insulin secretion, in others there actually may be excess production, at least in certain stages, but the net result is a relative deficiency because the demand exceeds the supply. The excess demand may be due to an increase in the body metabolism (e. g., thyrotoxicosis, pregnancy), to counteraction by other hormones (somatotropin, hydrocortisone, glucagon, and epinephrine), or to substances accumulating in the plasma which interfere with insulin action. There are at least three such plasma factors: (*a*) one in the γ-globulin fraction, presumably part of an immunological reaction to exogenous insulin, (*b*) one in the α-globulin fraction, appearing during diabetic acidosis, and (*c*) one in the lipoprotein fraction, apparently related to pituitary function.

Most of the therapy thus far has consisted of supplying more insulin and/or reducing the insulin requirements. Even the introduction of lente insulin preparations leaves much to be desired in the smooth control of the disease because there are so many variable factors which cannot be met by the homeostatic mechanisms such as exist in normals.

The accidental discovery of the hypoglycemic action of sulfonylureas led to the introduction of two of these compounds for the treatment of diabetes, carbutamide and tolbutamide. These drugs, which are slowly metabolized and long-acting, have a comparable effect in reducing hyperglycemia and glycosuria. Present evidence suggests that this is accomplished by stimulating an increased secretion of insulin and by decreasing the glucose output from the liver. It is possible that these sulfonylureas might also decrease glucagon secretion. They exert no hypoglycemic action in the total absence of the pancreas. Much more hypoglycemia is produced by their injection into the right gastroepiploic artery than into the femoral vein. With the doses used ordinarily they do not increase the effectiveness of insulin. Whereas an increased insulin secretion could account for some of the observed liver changes, such as decreased glucose output and decreased glucose-6-phosphate, sulfonylureas bring about changes, different from insulin, in blood pyruvate and lactate, in the conversion of fructose or galactose to glucose, and in other constituents. The sulfonylureas do not block increased glucose release from liver by glucagon or epinephrine, but under certain conditions these responses are somewhat modified.

Approximately 50% of diabetes patients show a relatively good response to sulfonylureas. This percentage can be modified markedly by the type of patient selected for treatment, age being the most important factor. Less than 10% of patients with juvenile diabetes respond, while more than 80% of those over 60 respond well. Another important correlation is the previously required insulin dosage—the smaller, the better the results with sulfonylurea. Some investigators have concluded, contrary to the conclusions of others, that good responses were also favored by obesity, stability of the diabetes, and recent onset of the disease. The selection of the appropriate patients for therapy is greatly assisted by subjecting the patient to a short (four-hour) test of hypoglycemic response to tolbutamide.

The results with carbutamide and tolbutamide are very gratifying in most of the patients who respond satisfactorily. The elderly respond best, and they are the ones who experience the greatest difficulty with insulin injections.

A recent survey of 7193 patients treated with carbutamide revealed that 5.36% experienced untoward reactions. Whereas many of the reactions were mild and tran-

sient, consisting of such things as headache, malaise, anorexia, and skin rashes, others were serious and included interstitial myocarditis, hepatitis, agranulocytosis, acute hemolytic anemia, purpura, and collagen-like disorders. Indeed, in 8 instances death has been attributed to carbutamide. These reactions are more numerous and severer than have been reported from Germany, where more than 40,000 patients have been treated and where a lower dosage regimen ordinarily has been used.

In the United States the reports accumulated thus far have indicated that untoward reactions have been much less prominent with tolbutamide than with carbutamide. Therefore, on the basis of present evidence, tolbutamide seems preferable, but careful continued study of this compound is required.

Since few patients are cured while under this treatment and because intermittent therapy might increase the incidence of toxic reactions, it is recommended that continuous therapy to given, usually using a maintenance dose only 1 gm., or less, per day. Insulin should also be used as indicated and the customary attention to diet, and other factors must be given.

Present investigations will most likely lead to the provision of new drugs, active orally, with even greater advantages.

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A Clinical Study in Hodgkin's Disease

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Introduction

This report is an analysis of clinical data derived from a study of 91 patients with Hodgkin's disease. Special attention was paid to the blood picture before therapy, the effects of therapy, and the prognostic significance of certain manifestations of Hodgkin's disease. No attempt has been made to review all the literature on this subject, as this has been done adequately in the past by others.[1-4] However, when indicated, appropriate references to the literature will be made.

Material

All patients referred to one of us (M. M. W.) during the 10½-year period from May 1, 1945, to Oct. 31, 1955, who had pathologically proved Hodgkin's disease are included in this series. The 91 cases thus available came from the Salt Lake County General Hospital and the Salt Lake Veterans Hospital and from various parts of Utah and neighboring states. At each visit to this clinic, a complete or interval history was taken, and physical examination, complete blood cell count, and other laboratory procedures that may have been indicated at the time were carried out on all patients.

In 81 cases the illness started some time after 1942, in 9 it appeared during 1942, and in 1 the onset was in 1940. Since all patients were alive in 1945 or thereafter, x-ray therapy, mechlorethamine hydrochloride (nitrogen mustard), sulfonamides, penicillin, and blood transfusions were available for all of them.

The mean age at onset of illness for the 91 cases is 31 years, with a median of 30 and a range of 2 to 68 years (Table 1). The peak incidence in five year groups is between 30 and 34 years of age (Fig. 1). No difference in age incidence was found between veteran and nonveteran males. The mean for the females is 4.4 years less than that for the males (Table 3, A).

The ratio of males to females for the entire group is 2.1:1. If the 14 males referred from the Veterans Hospital are excluded, the ratio is 1.7:1.

On Oct. 31, 1955, the tabular date, 61 of the patients were dead, 29 were alive, and 1 was lost to follow-up after 74 months of disease.

Methods and Definitions

General.—The date of "onset of illness" in the present study is the date of the first persistent symptom which, in retrospect, was probably due to Hodgkin's disease, e. g., lymph node enlargement, fever of unknown etiology, anorexia, weight loss, night sweats, or persistent cough with subsequent evidence of mediastinal or pulmonary involvement.

The cases have been classified according to the degree of dissemination of the disease (Table 2) as detected by the first physician consulted for symptoms due to Hodgkin's disease.

Statistical Methods and Definitions.—By considering "population at risk,"[5] it is possible to include all patients of a series in the calculation of survival: dead, alive, and those lost to follow-up. The per cent survival at a stated time is determined by dividing the number of patients known to be alive at that time by the number of patients in the series who are known to have been "exposed to the risk" of surviving that length of time. The numerator will obviously decrease with time and so will the denominator, but the latter will change at a slower rate than the former. The numerator decreases because of (*a*) elimination of patients who have died before the period of survival being considered (1, 2, 3, etc. years) and (*b*) exclusion of patients who may still be alive and of those who have been lost to follow-up but are not definitely known to have survived to the particular time. The demoninator declines because (*a*) patients who are alive at the tabular date or who were lost to follow-up after a certain period of time are considered to be at risk only for the interval from the onset of illness to the tabular date or to the time when they were lost to follow-

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TABLE 1.—*Age at Onset*

Subjects	No.	Mean	Median	Range
All males	62	32	31	2-68
Veterans	14	31	30	23-45
Nonveterans	48	32	31	2-68
Women	29	28	25	13-66
Total	91	31	30	2-68

up, but not thereafter, and (*b*) patients who are deceased are considered to be at risk only from the onset of illness to the tabular date but not thereafter.

A method employing the principle of "population at risk" is preferrable for analysis of survival data. However, many of the studies in the literature report the survival of only the deceased patients or, in addition, consider living patients to be dead at the tabular date. In order that our

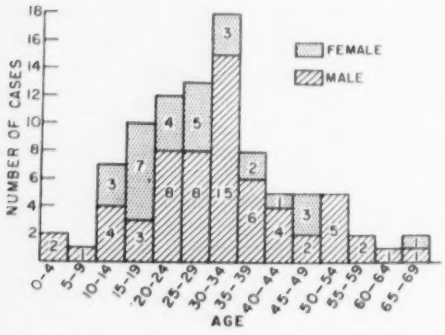

Fig. 1.—Age at onset in five-year intervals.

data may be compared with the results of such studies they have also been calculated by these methods.

Standard "*t*" tests and χ^2 were generally used. When exceptionally small numbers of cases were available White's nonparametric rank test[6] was employed. When the probability was 0.05 or less, this was considered to be statistically significant. The test used, factors involved and values obtained are all listed in Table 3. The letter appearing after each statistical statement in the text refers to the statistic in Table 3.

Results

Blood Picture Before Therapy.—Since many of the patients had received therapy before visiting this clinic and the accompanying notes were not always complete with regard to laboratory findings, hematologic data before therapy were not available for all patients in this series.

Volume of Packed Red Cells: Mild anemia at the altitude of Salt Lake City (4250 ft. above sea level) was arbitrarily defined as a volume of packed red cells of 38,000,000 to 42,000,000 per 100 ml. of blood in males and 35 to 40 in females. Values less than these were defined as moderate anemia. Data were available for 46 patients, of which 24 were anemic—14 mildly and 10 moderately. The proportion of males and females in each group was not significantly different.

Leukocytes: White blood cell counts were available for 47 cases, and in all but 4 of these there were also differential leukocyte counts. Leukocytosis (more than 10,000 leukocytes per cubic millimeter of blood) was present in 21; normal values, in 21, and leukopenia (less than 5000 leukocytes per cubic millimeter of blood), in 5 cases. The highest leukocyte count was 32,000 per cubic millimeter of blood and the lowest 1250. The absolute values for the various leukocytic elements are indicated in Table 4.

Platelets: An estimate of the number of platelets was available for only 32 patients. In 24 of these, the counts (Table 4) were made by the direct method (Rees-Ecker). Seven of these were between 401,000 and 563,000 platelets per cubic millimeter of blood, fourteen were within the normal

TABLE 2.—*Clinical Classification of Hodgkin's Disease*

Class I.	Involvement of only one lymph node region and no constitutional symptoms.
Class II.	A. Involvement of only one lymph node region but accompanied by constitutional symptoms.
	B. Involvement of two or more adjacent lymph node regions confined to either upper or lower trunk; with or without constitutional symptoms.
Class III.	Involvement of multiple lymph node regions with or without constitutional symptoms or acute Hodgkin's disease with no obvious lymphatic involvement.

TABLE 3.—*Statistics*

Statistic Letter	Problem	Factors Involved*	No. Patients	t	Value of χ^2	T'	Probability
A	Age at onset	Males	62	1.516			0.10-0.20
		Females	29				
B	Degree of response to therapy in Class II	Mechlorethamine hydrochloride: complete	2		1.432		0.20-0.30
		Partial and none	4				
		X-ray: complete	9				
		Partial and none	3				
C	Degree of response to therapy in Class III	Mechlorethamine hydrochloride: complete	6		0.016		0.90
		Partial and none	28				
		X-ray: complete	4				
		Partial and none	13				
D	Complete remissions in Class III	Mechlorethamine hydrochoride	6			30	>0.05
		X-ray	4				
E	Degree of response to therapy for all observations in the specified classes	I: complete	11		0.223		0.50-0.70
		Partial and none	3				
		II: complete	13				
		Partial and none	7				
F	Degree of response to therapy for all observations in the specified classes	II: complete	13		11.647		<0.01
		Partial and none	7				
		III: complete	14				
		Partial and none	46				
G	Degree of response to therapy for all observations in the specified classes	I: complete	11		16.128		<0.01
		Partial and none	3				
		III: complete	14				
		Partial and none	46				
H	5-yr. survival rate by sex	Males: alive	12		2.355		0.10-0.20
		At risk	42				
		Females: alive	8				
		At risk	16				
I	5-yr. survival rate in males by class	I: alive	3		0.020		0.80-0.90
		At risk	10				
		II: alive	6				
		At risk	17				
J	5-yr. survival rate in males by class	I: alive	3		0.009		0.90-0.95
		At risk	10				
		III: alive	3				
		At risk	15				
K	5-yr. survival rate in males by class	II: alive	6		0.321		0.50-0.70
		At risk	17				
		III: alive	3				
		At risk	15				
L	5-yr. survival rate in females by class	II: alive	6		0.000		>0.99
		At risk	11				
		III: alive	2				
		At risk	5				
M	Sex incidence in different classes	I and II: males	36		2.708		0.05-0.10
		Females	22				
		III: males	26				
		Females	7				
N	Survival to the tabular date	Dead	61	1.962			0.05
		Alive	30				
O	3-yr. survival from onset of illness in early- and late-treated groups of patients	0-5 mos.: alive	24		3.276		0.05-0.10
		At risk	44				
		12+mo.: alive	10				
		At risk	12				
P	5-yr. survival from onset of illness in early- and late-treated groups of patients	0-5 mo.: alive	12		0.089		0.70-0.80
		At risk	34				
		12+Mo.: alive	4				
		At risk	11				
Q	3-yr. survival from start of therapy in early- and late-treated groups of patients	0-5 mo.: alive	21		0.164		0.50-0.70
		At risk	44				
		12+mo.: alive	6				
		At risk	11				
R	5-yr. survival from start of therapy in early- and late-treated groups of patients	0-5 mo.: alive	12		0.004		0.95
		At risk	35				
		12+mo.: alive	3				
		At risk	11				
S	Sex incidence in the early- and late-treated groups of patients	0-5 mo.: females	15		0.044		0.80-0.90
		Males	38				
		12+mo.: females	5				
		Males	9				
T	Class distribution in the early- and late-treated groups of patients	0-5 mo.: Class III	23		2.250		0.10-0.20
		Classes I and II	30				
		12+mo.: Class III	3				
		Classes I and II	11				
U	5-yr. survival in patients with and without pruritus	Pruritus: alive	9		2.269		0.10-0.20
		At risk	19				
		No pruritus: alive	11				
		At risk	40				
V	Incidence of pruritus in the sexes	Pruritus: males	15		2.796		0.05-0.10
		Females	12				
		No pruritus: males	47				
		Females	17				
W	Incidence of mediastinal involvement in patients with and without pruritus	Pruritus with mediastinal	19		3.690		0.05-0.10
		Without mediastinal	8				
		No pruritus with mediastinal	31				
		Without mediastinal	33				

* T' refers to the value obtained in the rank test.

TABLE 4.—*Hematologic Data Before Therapy*

Determination	Normal Values	No. Normal	Incidence, %	No. Above Normal	Incidence, %	No. Below Normal	Incidence, %
Volume of packed RBC							
Males	>42	22	48	0	0	24	52
Females	>40						
Platelets/cu. mm.	200,000-400,000	14	58	7	29	3	13
Leukocytes/cu. mm.	5,000-10,000	21	45	21	45	5	11
Neutrophils/cu. mm.	2,500-5,800*	10	23	27	63	6	14
Eosinophils/cu. mm.	50-250*	13	30	14	33	16	37
Lymphocytes/cu. mm.	1,500-3,000*	25	58	1	2	17	40
Monocytes/cu. mm.	285-500*	10	23	17	40	16	37
E.S.R., mm./hr.		9	26	26	74	--	--
Males	0-9*						
Females	0-20						
Without anemia		4		10			
With anemia		5		16			

* These values were obtained from Wintrobe.[7]

range (200,000 to 400,000), and three were between 160,000 and 198,000. An estimate of platelets by examination of the stained smear alone was available for seven patients. In six cases, their number was "adequate," and in one it was "reduced." In addition to the patients referred to above, one may be added who was seen first at a Naval Hospital, where he was thought to have idiopathic thrombocytopenic purpura. His illness was not diagnosed as Hodgkin's disease until splenectomy had been performed and the sections of the spleen revealed the characteristic histologic findings.

Erythrocyte Sedimentation Rate: The method of Wintrobe was used. The frequencies of normal and elevated "uncorrected" values in cases with and without anemia are indicated in Table 4.

Frequency of Various Hematologic Findings Before Therapy: The percentage of patients with certain blood findings before institution of therapy is given in Table 4. It can be seen that elevation of the erythrocyte sedimentation rate, neutrophilia, and anemia are the commonest deviations from the normal. On the other hand, leukopenia is very uncommon, and a lymphocytosis (3600 per cubic millimeter of blood) was present in only one case.

Therapy.—Most of the therapy was prescribed for each patient by one of us (M. M. W.) on the basis of indications and contraindications which have been described elsewhere.[7]

Five hundred thirty-one courses of therapy were administered to the 90 patients for whom adequate information is available. These were as follows: 260 courses of mechlorethamine hydrochloride to 78 patients; 29 courses of TEM (triethylene melamine) alone to 14 patients; 212 courses of x-ray therapy alone to 67 patients; 24 courses of HN_2 plus x-ray therapy to 16 patients; and 1 course each of urethan, chlorambucal (CB 1348), potassium arsenite (Fowler's) solution, TEM plus x-ray therapy, radical thigh surgery plus HN_2, and radical neck surgery plus x-ray therapy and HN_2.

Four patients at the tabular date had not received mechlorethamine hydrochloride, and fourteen had not received x-ray therapy.

Most patients who die of Hodgkin's disease ultimately have widespread disease similar to that seen in Class III patients. It was possible, therefore, in most instance, to evaluate three responses to the first course of therapy in an original Class I patient, two in a Class II patient, and one in a Class III patient. Thus, 94 first courses of therapy could be evaluated in 77 patients.

The response to x-ray or mechlorethamine hydrochloride therapy was evaluated as to degree and duration. Three degrees of response were designated: (*a*) complete—complete disappearance of all signs or symptoms of the disease; (*b*) partial—appreciable decrease in organ and/or lymph node size as well as significant symptomatic improvement; (*c*) none—none or only slight decrease in organ or lymph node dimensions and no or only slight improvement is symptomatology, or any degree of response last-

TABLE 5.—*Response to Therapy*

Therapy	Response	Class in which first course of therapy was evaluated								
		Class I—14 Courses			Class II—20 Courses			Class III—60 Courses		
		No. Cases	Per Cent with This Response	Mean Duration, Mo.	No. Cases	Per Cent with This Response	Mean Duration, Mo.	No. Cases	Per Cent with This Response	Mean Duration, Mo.
Complete observations										
Mechlorethamine hydrochloride	Complete	2	100	13	2	33	15	6	18	9
	Partial	0	--	--	3	50	3	19	56	3
	None	0	--	--	1	17	--	9	26	--
X-ray	Complete	2	40	5	9	75	19	4	24	22
	Partial	3	60	19	2	17	2	10	59	3
	None	0	--	--	1	8	--	3	17	--
Combination	Complete	0	--	--	0	--	--	2	33	17
	Partial	0	--	--	0	--	--	4	67	3
	None	0	--	--	0	--	--	0	--	--
Incomplete observations										
Mechlorethamine hydrochloride	Complete	3	100	14	1	100	3	0	--	--
	Partial	0	--	--	0	--	--	0	--	--
	None	0	--	--	0	--	--	0	--	--
X-ray	Complete	1	100	9	1	100	8	0	--	--
	Partial	0	--	--	0	--	--	0	--	--
	None	0	--	--	0	--	--	0	--	--
Combination	Complete	3	100	22	0	--	--	2	67	73
	Partial	0	--	--	0	--	--	1	33	1
	None	0	--	--	0	--	--	0	--	--
All observations										
All therapy	Complete	11	79		13	65		14	23	
	Partial	3	21		5	25		34	57	
	None	0	--		2	10		12	20	

ing less than one month. Duration was expressed in months.

When less than two months had elapsed between the last dose of one form of therapy and the first dose of another, this course was designated as a combination of the two forms of treatment.

Table 5 is a complete tally of the results of the first courses of therapy in the three classes of disease. At the time of tabulation, 12 patients were still in remission following the course of therapy being evaluated. These 12 responses are listed separately as "incomplete observations." The per cent of complete, partial, and no remissions in all instances of each stage of disease is also indicated.

No significant difference was found in the degree or duration of response to mechlorethamine hydrochloride, x-ray, or combination therapy within each class (B,C,D). The three rows at the bottom of Table 5 indicate that the per cent of complete remissions decreased as the disease advanced. The difference between the frequency of complete remissions in Classes I and II is not significant(E), but the differences between Classes II and III and I and III are highly significant(F,G). Only two of the 91 patients showed complete resistance to all courses of x-ray or mechlorethamine hydrochloride therapy. Many of the remainder showed no response at times to one form of therapy but responded well to the other. Occasionally, patients at one time showed no response to either form of therapy but responded well to one or the other modality at a later date.

Survival.—Survival After Onset of Illness: Calculated from onset of illness and according to "population at risk," the survival at each year for males and females in the three classes of disease, as well as the over-all figures for each sex and for both sexes combined, are given in Table 6. Figure 2 was derived from Table 6 and graphically represents the survival for the entire series, as well as for males and females separately. The details of the number of males and females, dead or alive in each class, as well as the average survival in months, are given in Table 7.

From Table 6 it is observed that the five-year survival for the entire series is 35%.

TABLE 6.—*Survival from Onset of Illness*

Sex	Class		Years										
			0	1	2	3	4	5	6	7	8	9	10
M	I	Alive	14	13	11	7	4	3	2	0	0	0	0
		At risk	14	13	12	11	11	10	10	8	6	6	5
		Per cent	100	100	92	64	36	30	20	0	0	0	0
M	II	Alive	22	22	16	12	9	6	5	4	1	1	0
		At risk	22	22	20	19	18	17	15	14	11	9	8
		Per cent	100	100	80	63	50	35	33	29	9	11	0
M	III	Alive	26	19	12	8	5	3	3	2	2	1	0
		At risk	26	26	25	23	17	15	12	11	9	5	3
		Per cent	100	73	48	35	29	20	25	18	22	20	0
M	All	Alive	62	54	39	27	18	12	10	6	3	2	0
		At risk	62	61	57	53	46	42	37	33	26	20	16
		Per cent	100	89	68	51	39	29	27	18	12	10	0
F	I	Alive	4	4	3	0	0	0	0	0	0	0	0
		At risk	4	4	3	2	0	0	0	0	0	0	0
		Per cent	100	100	100	0	—	—	—	—	—	—	—
F	II	Alive	18	18	14	11	7	6	5	4	2	2	2
		At risk	18	18	16	14	11	11	10	10	10	10	8
		Per cent	100	100	88	79	64	55	50	40	20	20	25
F	III	Alive	7	5	4	4	4	2	2	1	1	1	0
		At risk	7	7	7	6	6	5	5	5	5	5	4
		Per cent	100	71	57	67	67	40	40	20	20	20	0
F	All	Alive	29	27	21	15	11	8	7	5	3	3	2
		At risk	29	29	26	22	17	16	15	15	15	15	12
		Per cent	100	93	81	68	65	50	47	33	20	20	17
Both	All	Alive	91	81	60	42	29	20	17	11	6	5	2
Both		At risk	91	90	83	75	63	58	52	48	41	35	28
Both		Per cent	100	90	72	56	46	35	33	23	15	14	7

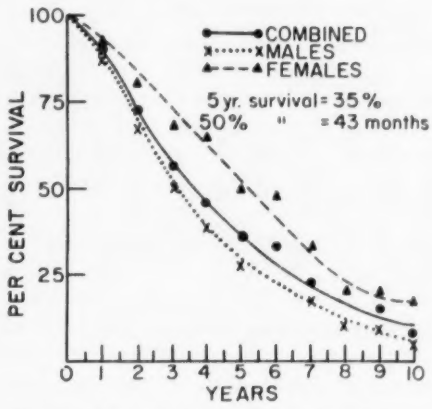

Fig. 2.—Survival from onset of illness.

The Tables indicate that the females lived longer than the males. The difference between a five-year survival of 50% for females and 29% for males is not statistically significant(H) but is suggestive. There was no significant difference in the survival of males in different classes (I,J,K), or of females in Classes II and III(L).

The ratio of females to males is higher in Classes I plus II than in Class III. This would suggest that females tend to have less widespread disease than males when they first seek the aid of a physician; however, the probability value(M), for the data is not low enough for this to be regarded as a statistically significant difference.

The mean survival to the tabular date of the living patients is seen in Table 7 to be longer than that of the patients who died. This difference is significant(N) and is due to a few long-term survivors in the living group.

Survival After Initiation of Therapy: The date of initiation of therapy was available for all but one patient. To study the influence on survival of the early and late initiation of therapy, the 90 cases were divided into three groups as follows: 0 to 5, 6 to 11, and 12 or more months of illness before therapy had been started. For each of these groups, survival from the "onset of illness" (Table 8) and from the initiation of therapy (Table 9) was calculated according to the concept of "population at risk." By combining male and female cases in each group and by using only the first and third groups, a clear-cut comparison of groups could be made. Rows 2 and 6 of Tables 8 and 9 contain these data and are graphically depicted in Figures 3 and 4, respectively.

From Figure 3 it is seen that the total survival is somewhat longer for those in whom therapy was delayed for a year or more as compared with those who were treated early; the difference in the number of three year survivals (55% versus 83%) does not, however, come within the range of statistical significance(O). Survival at

TABLE 7.—*Survival from Onset of Illness to the Tabular Date*

Class	Sex		No. Cases	Mean Survival, Mo.	Median Survival, Mo.	Range of Survival, Mo.
I	M	Dead	10	43	42	17-72
		Alive	4*	31	24	2-74
	F	Dead	1	36	36	36
		Alive	3	38	39	30-45
II	M	Dead	16	48	37	12-113
		Alive	6	42	33	17-86
	F	Dead	8	53	48	16-93
		Alive	10	55	44	16-123
III	M	Dead	21	21	16	5-53
		Alive	5	69	72	12-115
	F	Dead	5	31	18	5-80
		Alive	2	81	81	48-113
I, II, III	Both	Dead	61	36	35	5-113
		Alive	30*	52	44	2-123

* Includes one patient lost to follow-up.

TABLE 8.—*Survival from Onset of Illness According to Duration of Illness Before Initiation of Therapy*

Row	Interval Before Therapy, Mo.	Sex	No.		Years 0	1	2	3	4	5	6	7	8	9	10
1	0-5	M	38	Alive	53	43	32	24	18	12	11	5	4	3	1
		F	15	At risk	53	52	48	44	38	34	29	26	22	18	16
2				Per cent	100	82	67	55	47	35	38	19	18	17	6
3	6-11	M	14	Alive	23	23	15	10	3	3	3	3	2	1	0
		F	9	At risk	23	23	21	18	13	12	11	11	10	8	4
4				Per cent	100	100	71	56	23	25	27	27	20	13	0
5	12+	M	9	Alive	14	14	13	10	7	4	3	3	1	1	1
		F	5	At risk	14	14	13	12	11	11	11	11	9	9	9
6				Per cent	100	100	100	83	64	36	27	27	11	11	11

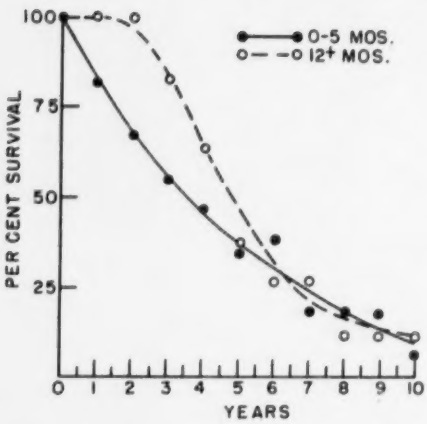

Fig. 3.—Survival from onset of illness according to the interval before initiation of therapy.

five years was not significantly different (P). Once therapy was instituted (Fig. 4), there was no significant difference in survivals (Q,R).

In attempting to find a possible cause for the somewhat longer survival in the late-treated group as compared to the early group of patients, the class distribution within each group was examined. In the early-treated group there were 38 males and 15 females. Classes I, II, and III were represented 9:21:23. In the late-treated group there were 9 males and 5 females, and Classes I, II, and III were represented 2:9:3. The difference between the ratios of males to females in the two groups is not significant (S). However, 43% of the early-

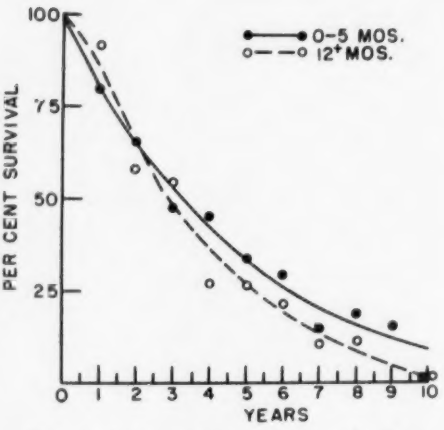

Fig. 4.—Survival from initiation of therapy according to the interval before therapy was instituted.

TABLE 9.—*Survival After Therapy According to Duration of Illness Before Initiation of Therapy*

Row	Interval Before Therapy, Mo.		Years 0	1	2	3	4	5	6	7	8	9	10
1	0-5	Alive	53	41	31	21	17	12	9	4	4	3	0
		At risk	53	51	48	44	37	35	30	27	22	19	15
2		Per cent	100	80	65	48	46	34	30	15	18	16	0
3	6-11	Alive	23	15	13	3	3	3	3	2	1	0	0
		At risk	23	21	19	13	13	12	11	10	8	5	2
4		Per cent	100	71	69	23	23	25	27	20	13	0	0
5	12+	Alive	14	12	7	6	3	3	2	1	1	0	0
		At risk	14	13	12	11	11	11	9	9	9	7	5
6		Per cent	100	92	58	55	27	27	22	11	11	0	0

treated group were in Class III, whereas only 21% of the late-treated group were in Class III. This difference may suggest(T) that patients with more widespread disease were treated earlier than those with more localized disease. This must be borne in mind in evaluating the significance of Figures 3 and 4.

Three-quarters of the 91 patients in this series consulted a physician within three months from the onset of illness. All but four patients consulted a physician within five months after the onset of illness, and only one of these cases was included in the late-treated group of patients. This indicates that the greater portion of the year or more of delay before starting therapy in the late-treated group occurred after the physician was consulted rather than before.

Prognostic Significance of Various Manifestations of Hodgkin's Disease.—In the past, clinicians have indicated that the appearance of various manifestations of Hodgkin's disease has some bearing on prognosis. Nevertheless, there have been very few systematic studies which were designed to establish or refute these impressions. In the present study, 16 different manifestations of Hodgkin's disease were analyzed from three different standpoints.

In relation to each manifestation which was studied, any one of the 91 cases was included in which at any time during the course of the illness such involvement had been present. A single case may, therefore, have been included in from 1 to all 16 of the groups studied. The date of onset of each manifestation was taken as the date of the first clinical sign or symptom due to the manifestation.

In relation to pruritus, it should be pointed out that this term has been used to refer to unexplained itching over areas of the body where no skin lesions were present. The term "fever" as used here refers to the situation in which, after careful investigation, an infectious process had been satisfactorily ruled out. Patients who manifested no anemia 6 weeks after a course of therapy but who did develop persistent anemia 12 or more weeks after treatment have been considered to have developed "anemia after therapy" but not directly due to therapy.

The survival from the onset of a specific manifestation was determined for each of the 16 groups of patients. These data are presented in Table 10 and are graphically depicted in Figure 5. The survival from the onset of illness was similarly determined for each of the 16 groups and is described in Table 11 and Figure 6. A horizontal line drawn across Figures 5 and 6 at the 50% survival level intersects each curve at a point corresponding to the median survival in patients with each manifestation. The data thus derived from Figures 5 and 6 appear in Columns 1 and 2 of Table 12. Column 3 of this Table contains the values for the per cent of the total survival following the onset of each of the manifestations discussed. Each figure was obtained by dividing the value in Column 1 by that in Column 2 and multiplying by 100.

From Column 1 of Table 12 it is seen that after the appearance of skin infiltration, following the appearance of moderate anemia before or after therapy, or after the appearance of leukopenia before therapy, the average survival was seven months or less. On the other hand, the survival after the appearance of pruritus or mediastinal involvement was about two and one-half years. Once the disease extended into the lung parenchyma, however, the average survival was but one year.

The median survival from the onset of illness for the entire series of 91 patients was three and one-half years. In patients with leukopenia or moderate anemia before therapy the total survival was approximately one year. In patients with leukocytosis or skin infiltration, the total survival was relatively short, being only two to two and one-half years.

From Column 3 it is seen that moderate anemia after therapy and skin infiltration

TABLE 10.—*Survival from Onset of Specific Manifestation*

Manifestation		Years										
		0	1	2	3	4	5	6	7	8	9	10
Mediastinum	Alive	50	41	21	16	10	8	7	6	3	2	0
	At risk	50	49	45	40	34	30	26	23	21	15	12
	Per cent	100	84	47	40	29	27	27	26	14	13	0
Lung parenchyma	Alive	34	17	11	9	4	3	3	2	2	1	0
	At risk	34	33	30	27	25	22	22	20	16	9	4
	Per cent	100	52	37	33	16	14	14	10	13	11	0
Palpable spleen	Alive	45	22	14	5	4	2	1	1	0	0	0
	At risk	45	44	41	36	33	31	22	19	16	10	7
	Per cent	100	50	34	14	12	6	4	5	0	0	0
Enlarged liver	Alive	40	17	7	3	2	2	0	0	0	0	0
	At risk	40	38	36	31	28	23	16	13	9	5	4
	Per cent	100	45	19	10	7	9	0	0	0	0	0
Pruritus	Alive	27	21	15	10	4	4	--	--	--	--	--
	At risk	27	25	23	20	17	16	--	--	--	--	--
	Per cent	100	84	65	50	24	25	--	--	--	--	--
Skin infiltration	Alive	4	0	0	0	0	0	--	--	--	--	--
	At risk	4	3	2	2	2	2	--	--	--	--	--
	Per cent	100	0	0	0	0	0	--	--	--	--	--
Bone	Alive	16	7	2	2	1	1	--	--	--	--	--
	At risk	16	15	14	12	10	10	--	--	--	--	--
	Per cent	100	47	14	17	10	10	--	--	--	--	--
Fever	Alive	57	29	15	7	5	4	4	3	1	1	0
	At risk	57	54	52	44	37	32	26	25	21	16	13
	Per cent	100	54	29	16	14	13	15	12	5	7	0
Mild anemia before therapy	Alive	14	8	5	2	1	1	--	--	--	--	--
	At risk	14	12	11	9	7	6	--	--	--	--	--
	Per cent	100	67	45	22	14	17	--	--	--	--	--
Moderate anemia before therapy	Alive	10	1	0	0	0	0	--	--	--	--	--
	At risk	10	9	9	8	6	6	--	--	--	--	--
	Per cent	100	11	0	0	0	0	--	--	--	--	--
WBC before therapy >19,000	Alive	6	3	2	0	0	0	0	0	0	0	0
	At risk	6	4	3	1	0	0	0	0	0	0	0
	Per cent	100	75	67	0	--	--	--	--	--	--	--
WBC before therapy 10,000 to 18,900	Alive	15	9	5	3	1	0	0	0	0	0	0
	At risk	15	11	10	8	6	6	4	4	4	2	2
	Per cent	100	82	50	38	16	0	0	0	0	0	0
WBC before therapy 5,000 to 9,900	Alive	21	14	10	4	3	2	0	0	0	0	0
	At risk	21	19	18	14	11	9	8	6	5	3	1
	Per cent	100	74	56	29	27	22	0	0	0	0	0
WBC before therapy <5,000	Alive	5	1	0	0	0	0	--	--	--	--	--
	At risk	5	5	5	4	4	4	--	--	--	--	--
	Per cent	100	20	0	0	0	0	--	--	--	--	--
Mild anemia after therapy	Alive	10	5	3	1	1	0	--	--	--	--	--
	At risk	10	7	7	6	6	6	--	--	--	--	--
	Per cent	100	71	43	17	17	0	--	--	--	--	--
Moderate anemia after therapy	Alive	19	5	3	2	1	1	1	1	0	0	0
	At risk	19	19	19	15	15	12	10	8	7	4	2
	Per cent	100	26	16	13	7	8	10	13	0	0	0

appear to presage a serious turn of events, since 87% of the total survival in the average patient had already transpired before these signs appeared. Similarly, bone and parenchymal lung involvement may be considered to have been relatively late manifestations of Hodgkin's disease.

The data suggest that the appearance of pruritus is not an ill omen. In these patients the five-year survival was 47%, while that for those without pruritus was 28%. Although it is not possible to be certain about the statistical significance of this difference(U), it is clear at least that the presence of pruritus does not in itself signify rapid progression of the disease. It is possible, although not statistically certain(V) that females tend to develop this symptom more often than males. The ratio of females to males was 1:1.25 among patients with pruritus and 1:2.8 in patients without it. It may be added that the disproportionately high incidence of females with this manifestations does not explain the more favorable survival of the entire group with pruritus, since the survival curves for the

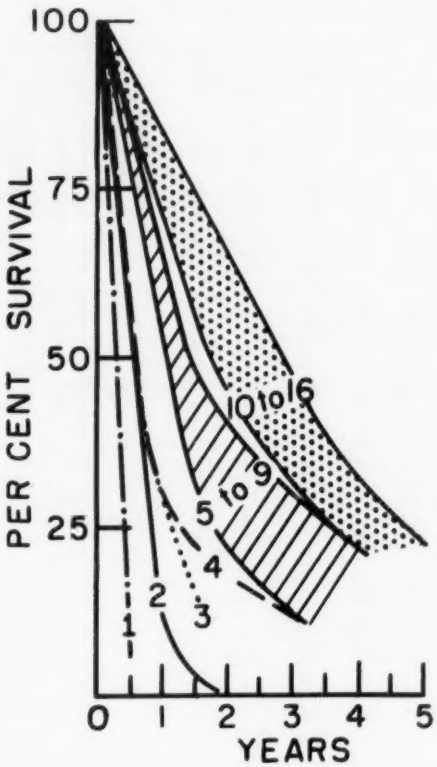

Fig. 5.—Survival from onset of a specific manifestation (numbers refer to those on chart): *1*, skin involvement; *2*, moderate anemia after therapy; *3*, moderate anemia before therapy; *4*, leukopenia; *5*, bone involvement; *6*, liver involvement; *7*, splenomegaly; *8*, fever; *9*, lung parenchymal involvement (*5-9* included in hatched area) *10*, mild anemia after therapy; *11*, mild anemia before therapy; *12*, marked leukocytosis; *13*, normal leukocyte count; *14*, mild leukocytosis; *15*, mediastinal involvement; *16*, pruritus (*10-16* included in stippled area).

males and females with pruritus were practically identical, as were the five-year survival rates (60% and 64%, respectively). It is of interest that the mediastinum was involved in 70% of the patients with pruritus, whereas only 48% of the patients without this symptom had mediastinal adenopathy. It would be of interest to know whether this difference is significant. Our data are only suggestive(W).

Other possible interrelationships are apparent from Table 12. Thus, all of the five patients with leukopenia also had moderate anemia before therapy. Four of the five patients with leukopenia and moderate anemia had enlarged spleens at the time the blood cell counts were performed, and in the fifth this organ was found to be involved at postmortem examination. Of the 45 patients with splenic involvement, 37 also had fever. It is of interest that eosinophilia, pruritus, and infiltration of the skin showed no inter-relationship.

Comment

Age at Onset and Sex.—The peak age incidence of 30 to 34 years with a mean of 31 years in the present series is in general agreement with most of the literature.[2,8-21,23-25] The females in the present series were from four to six years younger that the males, which is in accord with the observation [25] that in recent years a younger female population has been affected with Hodgkin's disease. The ratio of males to females of about 2:1 in this series is similar to that found in the literature,[1-3,8-13,15-19,21-25] where the usual figures are between 1.5 to 2.6:1. Only in one series [14] was the ratio found to be equal (1:1), and in another [20] it was found to be reversed.

Blood Picture in Hodgkin's Disease.—Many general statements have been made, [3,16,20] but few data have been published regarding the blood picture in Hodgkin's disease. In 1914, Bunting [26] indicated that a diagnosis of Hodgkin's disease could be made almost on the basis of the stained blood smear alone. He called attention to the presence of increased platelets and "transitional cells." His observations were later refuted by McAlpin.[27]

In general, our findings are similar to those of Uddströmer,[18] Sears,[28] and Wiseman.[29] The latter emphasized the increase in the monocyte: lymphocyte ratio and stated that he had not had a single case with an increased number of lymphocytes. We have found that elevation of the ESR, neutrophilia, and anemia occur very frequently in Hodgkin's disease before therapy (Table 4), and leukocytosis, monocytosis, and lympho-

TABLE 11.—*Survival from Onset of Illness in Patients Who Develop a Specific Manifestation*

Manifestation		Years										
		0	1	2	3	4	5	6	7	8	9	10
Mediastinum	Alive	50	47	35	29	19	12	12	9	4	3	1
	At risk	50	50	47	43	37	35	32	28	24	21	18
	Per cent	100	94	74	67	51	34	38	32	17	14	6
Lung parenchyma	Alive	34	34	30	23	15	11	7	7	4	3	2
	At risk	34	34	33	32	28	25	24	23	22	20	16
	Per cent	100	100	91	72	54	44	29	30	18	15	13
Palpable spleen	Alive	45	37	29	23	12	7	6	3	1	1	1
	At risk	45	45	45	43	36	32	29	27	23	18	16
	Per cent	100	82	64	53	33	22	21	11	4	6	7
Enlarged liver	Alive	40	32	24	19	13	9	6	5	1	1	0
	At risk	40	40	39	36	33	30	24	22	17	13	12
	Per cent	100	80	62	53	39	30	25	23	6	8	0
Pruritus	Alive	27	27	23	17	14	9	8	6	3	3	2
	At risk	27	27	26	24	20	19	16	16	15	15	13
	Per cent	100	100	88	71	70	47	50	38	20	20	15
Skin infiltration	Alive	4	4	2	0	0	0	0	0	0	0	0
	At risk	4	4	4	4	3	2	2	2	2	2	2
	Per cent	100	100	50	0	0	0	0	0	0	0	0
Bone	Alive	16	15	12	9	3	3	3	2	1	1	0
	At risk	16	16	16	15	12	11	11	11	10	8	5
	Per cent	100	94	75	60	25	27	27	18	10	12	0
Fever	Alive	57	48	32	22	11	8	6	4	1	1	1
	At risk	57	57	55	50	43	39	34	31	24	21	18
	Per cent	100	84	58	44	26	21	18	13	4	5	6
Mild anemia before therapy	Alive	14	12	8	7	3	2	--	--	--	--	--
	At risk	14	14	14	11	8	7	--	--	--	--	--
	Per cent	100	86	57	64	38	29	--	--	--	--	--
Moderate anemia before therapy	Alive	10	4	1	1	0	0	--	--	--	--	--
	At risk	10	10	9	8	6	6	--	--	--	--	--
	Per cent	100	40	11	13	0	0	--	--	--	--	--
WBC before therapy >19,000	Alive	6	4	2	1	0	0	0	0	0	0	0
	At risk	6	6	5	2	0	0	0	0	0	0	0
	Per cent	100	67	40	50	--	--	--	--	--	--	--
WBC before therapy 10,000 to 18,900	Alive	15	12	7	5	3	1	0	0	0	0	0
	At risk	15	14	12	12	8	7	4	4	4	3	2
	Per cent	100	86	58	42	38	14	0	0	0	0	0
WBC before therapy 5,000 to 9,900	Alive	21	18	13	9	4	2	1	0	0	0	0
	At risk	21	21	19	16	12	9	8	6	5	5	4
	Per cent	100	86	68	56	33	22	13	0	0	0	0
WBC before therapy <5,000	Alive	5	3	1	1	0	0	--	--	--	--	--
	At risk	5	5	5	4	4	4	--	--	--	--	--
	Per cent	100	60	20	25	0	0	--	--	--	--	--
Mild anemia after therapy	Alive	10	10	9	8	6	5	--	--	--	--	--
	At risk	10	10	9	8	7	7	--	--	--	--	--
	Per cent	100	100	100	100	86	71	--	--	--	--	--
Moderate anemia after therapy	Alive	19	19	14	11	6	4	3	1	0	0	0
	At risk	19	19	19	19	18	16	15	14	12	10	8
	Per cent	100	100	74	58	33	25	20	7	0	0	0

penia are not uncommon. Eosinophils are generally present and may be increased in number. The presence of eosinophils may aid in the diagnosis of Hodgkin's disease when the differential diagnosis rests between this disease and an acute bacterial infection. On the other hand, the presence of lymphocytosis may be considered to be strong evidence against a diagnosis of Hodgkin's disease.

Comparison of Effects of Mechlorethamine Hydrochloride and X-Ray Therapy.—Previous attempts to compare the effect of mechlorethamine hydrochloride and x-ray therapy on survival in Hodgkin's disease [25,39] have not demonstrated any advantage of one agent over the other. Similarly, our data (Table 5) do not indicate that one form of therapy is capable of inducing longer or more satisfactory remissions that the other. This observation is of interest, since sometimes the time consumed and the cost involved in the use of mechlorethamine hydrochloride are considerably less than in the case of x-ray therapy.

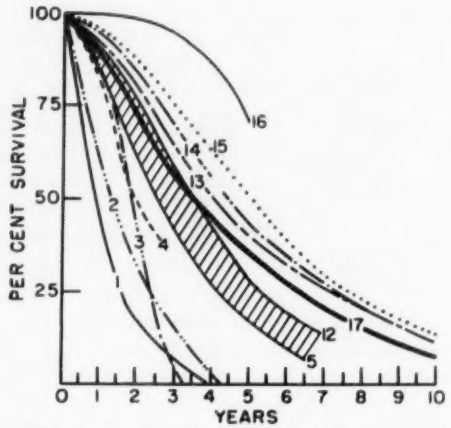

Fig. 6.—Survival from onset of illness in patients who developed the following specific manifestations (numbers refer to those on chart): *1*, moderate anemia before therapy; *2*, leukopenia; *3*, skin involvement; *4*, marked leukocytosis; *5*, mild leukocytosis; *6*, liver involvement; *7*, splenomegaly; *8*, fever; *9*, normal leukocyte count; *10*, bone involvement; *11*, mild anemia before therapy; *12*, moderate anemia after therapy (*5-12* included in hatched area); *13*, mediastinal involvement; *14*, lung parenchymal involvement; *15*, pruritus; *16*, mild anemia after therapy; *17*, entire series.

Survival.—Survival after Onset of Illness: Table 13 shows the survival from clinical onset of disease as recorded in several representative case studies in the literature. To make comparisons possible the three commonly employed methods of expressing survival are presented. There are serious objections to the analysis of survival on the basis of dead patients alone or by considering living patients to be dead at a tabular date. It was shown in the analysis of our own series that the mean survival of the living patients who were considered to be dead at the tabular date was longer than that of the dead patients (Table 7); this was due to the inclusion in the former group of a few long-term survivors. Exclusion of living patients in this series would have given an artifically low survival rate. This fact helps to emphasize the importance of using all patients in a study of survival rather than a select few. Considering living patients to be dead at a tabular date in itself prejudices these figures toward a lower survival rate. Of the three methods of analysis presented in Table 13, that in which the "population at risk" was considered probably expresses the true state most closely.

In general, survival in the present series has been about the same as that in the other series listed in Table 13.

The series of Peters, however, shows an exceptionally long survival. This rather marked discrepancy with the rest of the literature has been noted previously [25] and has not yet been explained.

Our data suggest that the prognosis in females may be somewhat better than in males. This does not agree with the findings of some authors,[14,22] but corroborates those of others.[3,9,16,20,25,31,32] In our series, as in

TABLE 12.—*Prognostic Significance of Specific Manifestations*

	Column						
	1 Median Survival, Mo. (Figs. 5 and 6)		3 Per Cent Total Survival with Each Manifestation	4 No. Males	5 No. Females	6 No. Patients	7 Per Cent Patients
Manifestation	From Onset of Manifestation	From Onset of Illness					
Skin infiltration	3	23	13	4	0	4	4
Moderate anemia after therapy	6	42	14	17	2	19	..
Moderate anemia before therapy	6	10	60	8	2	10	22
Leukopenia	7	15	47	4	1	5	11
Bone	11	39	28	11	5	16	18
Liver	11	35	31	32	8	40	44
Spleen	13	35	37	32	13	45	49
Fever	13	35	37	44	13	57	63
Lung parenchyma	13	52	25	25	11	34	37
Mild anemia after therapy	22	71	31	3	7	10	..
Mild anemia before therapy	22	40	55	7	7	14	30
Marked leukocytosis	24	24	100	2	4	6	13
Normal leukocyte count	27	35	77	14	7	21	45
Mild leukocytosis	29	31	94	10	5	15	32
Mediastinum	29	48	60	31	19	50	55
Pruritus	34	60	57	15	12	27	30

TABLE 13.—*Survival from Onset of Symptoms*

Method	Author	Study Period, Yr.	5-Year Survival	
			Alive/At Risk	Per Cent
Population at risk (life table)	Craft[24]	1926-1939	30/128	23
	Peters[9]	1924-1942	58/113	51
	Merner et al.[11]	1926-1942	33/160	33
	Smetana et al.[23]	1941-1946	?	33
	Shimkin et al.[29]	1914-1951	61/230	27
	Jelliffe et al.[14]	1930-1952	50/172	29
	Present series	1945-1955	20/58	35
			Mean survival, mo.	
Dead plus alive to the tabular date	Schreiner et al.[31]	Before 1924	31	
	Shimkin et al.[34]	1914-1951	44	
	Present series	1945-1955	41	
Dead only	Desjardins et al.[8]	1915-1920	31	
	Nathanson et al.[21]	Before 1933	30 (median)	
	Goldman et al.[22]	1926-1936	32	
	Present series	1945-1955	36	

others [16,25] a greater proportion of females than males had more localized disease at the initial examination. The reason for these differences is unexplainable at present. It has been suggested that the sex hormones [25,33] may play a role, but, to date, there is no evidence to support this suggestion. Estrogens and orchiectomy have been suggested as possible forms of therapy for males with Hodgkin's disease. For obvious reasons, one would not recommend the latter procedure without better evidence, but the experimental use of estrogen therapy might be considered.

Survival After Initiation of Therapy: Those patients in whom a relatively long period of time elapsed before the initiation of therapy survived longer than those patients who were treated early. The former patients, however, by and large represented persons in whom the disease was initially more localized.

This observation can be explained in several ways. The simplest explanation may be that too few patients have been studied to draw any valid conclusions. Another may be that since patients with localized involvement have a more slowly progressive form of the disease they might naturally survive for a longer time. These patients probably do not impress physicians as cases which require immediate therapy, and therefore a rather long interval elapses before therapy is initiated. Once the signs and symptoms of the disease arouse the patient and physician to some form of action, the progress thereafter is the same for all patients (Fig. 4). A third possibility is that certain forms of present-day "therapy" may actually shorten the lives of these patients. This concept is, of course, difficult to reconcile with the rapid clinical improvement in patients with Hodgkin's disease which follows shortly after a course of therapy.

Since radical local surgery was employed in the treatment of only two of our patients, this type of "early therapy" could not be evaluated. Most of the delay before initiating therapy in our series occurred after the physician was consulted rather than before. Therefore, it would seem that if the hope for long survivals or even cures in Hodgkin's disease does actually lie in early therapy,[2,3,31,34] then realization of this hope depends to a considerable extent upon the first physician consulted for symptoms due to Hodgkin's disease.

Prognosis.—Systematic studies have been made in regard to the prognostic significance of various manifestations of Hodgkin's disease by Bethell [12] and concerning the significance of bone involvement by Dresser and Spencer [35] and Vieta et al.[36]

According to our own observation, infiltration of the skin is a late manifestation, and once it occurs it is a bad prognostic sign. Anemia after therapy also occurs late in the disease and when several is also a bad prognostic sign, the latter being associated, on the average, with only a six-

month survival thereafter. Similar findings have been noted by Desjardins.[37]

Our data indicate that leukopenia and moderate anemia before therapy are not necessarily late signs of Hodgkin's disease; however, they are associated with a short total survival and appear to be bad prognostic signs. Bethell [12] has made the same observation. The occurrence of splenomegaly in four of the five patients with leukopenia and moderate anemia in our series, as well as the finding of splenomegaly in 14 of the 15 patients discussed by Riley and Gailland,[38] suggest that the spleen plays a role in maintaining the low levels of these elements in the blood. The occurrence of thrombocytopenic purpura in this disease, which had been cured by splenectomy in one of our patients as well as in a few in the literature,[39,40] lends some support to this hypothesis.

The survival from onset of illness in patients with leukocytosis was somewhat shorter than in patients with normal leukocyte counts. This was more apparent in patients with marked than in those with mild leukocytosis. This observation is in general agreement with observations recorded in the literature.[3,12,29,41]

Although the median survival of 39 months for patients who developed bone involvement is about the same as the median for the entire series (43 months), it is noteworthy that once bone involvement occurred, the survival was short (11 months). Dresser and Spencer found almost identical values in their study and the observations of Vieta et al. were similar.

In our series, patients with pruritus seemed to live longer than those without this peculiar symptom. Hoster et al.[3] listed marked pruritus as a poor prognostic sign, but Bethell [12] subsequently showed that 36% of patients with pruritus survived five years, whereas only 17% of those without this symptom survived five years. We have found no correlation between pruritus and eosinophilia, a subject which is in dispute in the literature.[1,16,18,42]

Summary and Conclusions

Data derived from the study of the 91 patients with Hodgkin's disease seen at this clinic from 1945 to 1955 are presented.

The hematologic findings before therapy revealed that an elevated erythrocyte sedimentation rate, leukocytosis, neutrophilia, monocytosis, lymphopenia, and anemia are common findings, whereas leukopenia is uncommon and lymphocytosis is very rare.

There was no demonstrable difference between the efficacy of x-ray and mechlorethamine hydrochloride in the treatment of this disease.

The five-year survival of the entire series was 35%, and the median survival was 43 months. Survival in females may have been longer than in males. Our data do not support the impression that early x-ray or mechlorethamine hydrochloride therapy prolongs life in patients with Hodgkin's disease.

A systematic study of the prognostic significance of various manifestations of Hodgkin's disease revealed that leukopenia before therapy, skin infiltration, and moderate anemia are bad prognostic signs. Skin involvement, moderate anemia after therapy, and bone and parenchymal lung involvement occur late in the course of the disease. The total survival in patients with leukopenia, moderate anemia before therapy, marked leukocytosis, or skin infiltration was relatively short. On the other hand, the total survival in patients who developed pruritus was somewhat longer than that in other groups.

Leukopenia and moderate anemia before therapy were associated with splenomegaly. Pruritus and mediastinal involvement were frequently present in the same patient.

Drs. Joseph C. Salvatore and Gerard G. Newman, of the Department of Preventive Medicine of the University of Utah, aided in the statistical analysis of these data. Misses Doris Kurth, Megan Scott, and Gwen Trappett gave assistance in performing the blood cell counts. The Mustargen (HN_2) used in this study was supplied by Dr. Frederick K. Heath, of Sharp & Dohme, Division of Merck & Co., Inc., Philadelphia.

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Editorials

The Clinical Use of Antibiotics in Combination

At a recent informal meeting of a large group of internists who are leaders in the field of infectious diseases, held in connection with the Central Society for Clinical Research, unanimous concern over the increasing numbers of antibacterial agents packaged in combination for oral or intramuscular use was expressed.

The accompanying editorial was suggested at this meeting. While American physicians owe a great debt of gratitude to the drug houses of this country for the quality of their products, there can be no question that the trend toward promotion of combination preparations of this type is a dangerous one. The reasons for this are outlined in the following combined statement. It is recognized that physicians have the opportunity to use combinations of single antibiotics in any way they think best, but availability of the scores of antibacterial products already put up in combinations decided upon by the manufacturer and not arranged for each individual patient will unquestionably lead to abuses if unchecked.

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The recent appearance on the market of preparations containing two antibiotics in the same capsule calls for an appraisal of the rationale of such therapy. Theoretical or practical reasons for administering more than one antibiotic to a patient at one time are as follows:

1. A second antibiotic may delay the emergence of bacteria resistant to the first antibiotic.
2. Two antibiotics may be synergistic with one another.
3. In the initial emergency treatment of seriously ill patients where the establishment of an etiological diagnosis and appropriate antibiotic sensitivity tests may be delayed, two or more drugs may properly be used as "insurance."
4. Mixed infections caused by more than one micro-organism may be better treated by antibiotics found most effective against each one.
5. Reduction of dosage of each of two "additive" drugs may result in lowered incidence of toxic effects to each, as in the case of streptomycin-dihydrostreptomycin.

The emergence of streptomycin-resistant tubercle bacilli is delayed when aminosalicylic acid or isoniazid is given in conjunction with streptomycin. In the realm of nontuberculous bacterial infections the application of this principle is not so clear. Numerous clinical-epidemiological studies have shown that the introduction of a new antibiotic into a hospital or a community is frequently followed by an increase in staphylococci resistant to that antibiotic. An attempt to prevent the development of antibiotic-resistant staphylococci by employing a combination in the treatment of ordinary bacterial infections was carried out during the winter of 1955-1956, employing novobiocin and spiramycin. In this study the emergence of staphylococci resistant to both these antibiotics was somewhat delayed, but after a few months bacteria resistant to both of them were easily found. In any event, the strain must be originally sensitive to the individual antibiotics if the combination is to delay or depress the development of resistance to any of them when they are used together.

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The Case for and Against Synergism

Penicillin and streptomycin have a synergistic effect against enterococcus and probably against penicillin-sensitive viridans Streptococcus as well. Also, laboratory evidence of synergism of various combinations of drugs against individual strains of several microbial species has been published, but much remains to be done before these studies can be applied at the clinical level. Furthermore, different combinations would seem to be synergistic against different species or even against different strains within the same species.

There is some clinical evidence that tetracycline derivatives or tetracycline in combination with streptomycin result in a lower relapse rate in the treatment of brucellosis than occurs with either drug alone. If the treatment period with a tetracycline is greatly prolonged, however, a similar low relapse rate will be achieved.

The "Insurance" Principle

In the treatment of serious staphylococcal and other infections the life of a patient may be jeopardized by withholding treatment until a satisfactory etiological diagnosis can be obtained or until antibiotic sensitivity tests are completed. In such situations the employment of more than one antibiotic is frequently justified, but these should be used in full doses.

Diminished Toxic Effects

When equal amounts of streptomycin and dihydrostreptomycin are administered, an additive therapeutic effect is obtained. The toxic effect of streptomycin is chiefly upon the vestibular portion of the eighth cranial nerve, whereas dihydrostreptomycin affects the auditory portion. When a 50-50 combination is used, diminished toxicity results without loss of therapeutic efficacy.

The question may be asked: "Why not use combinations since they do no harm?" Possible harmful effects are five in number. First, the use of fixed combinations of antibiotics tends to encourage inadequate therapy. Though suboptimal doses of each of two antibiotics may occasionally provide a synergistic action against certain strains of bacteria, it certainly cannot be assumed that more can ordinarily be accomplished by suboptimal than by optimal amounts of therapy. Nor is there any evidence that the spectrum of activity will be broadened beyond that provided by the type and amount of individual antibiotics actually administered. Hypersensitivity and toxicity may be expected to increase when two drugs are used instead of one; furthermore, when a physician encounters a toxic effect, such as a rash, he will not know which of the drugs was responsible. A third harmful effect is the probable development of bacteria resistant to either or both of the drugs used in the combination. And the fourth, a direct corollary of the second, is the accumulation of antibiotic-resistant microbes within hospitals or other semiclosed communities. The fifth is that if this trend is not checked now, the practicing physician will soon be confronted with such a bewildering array of antibiotic combinations supported by multicolored promotional material piling up daily upon his desk that rational chemotherapy will give way to chaos.

The indications for the use of combined antibiotics all apply to clinical situations which at the present time demand selection of specific doses for individual cases. The one exception is the streptomycin-dihydrostreptomycin combination.

There are no data or experience which would justify the employment of any fixed combination of two antibiotics in a single ampule or a single tablet or capsule for systemic use. It is our firm conviction that the promotion and sale of such combinations should be discouraged until and unless adequate data from controlled clinical investigation justify this practice, and then only with respect to definite combinations for specific purposes.

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Pneumococcal Endocarditis, Meningitis, and Rupture of the Aortic Valve

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The advent of an effective prophylactic and therapeutic agent may alter significantly both the incidence and etiology of a given anatomical lesion, and such may be the effect of penicillin upon aortic valvular disease. As a result of its use in the treatment of early syphilis, syphilitic disease of the aortic valve is seen with lessening frequency, and it is altogether possible that the widespread employment of penicillin as a prophylactic against rheumatic fever may result in a decrease in aortic valvular disease of rheumatic origin. Concomitant with the decline of two of the major causes of aortic valvular disease, lesions of other etiologies will acquire relatively greater significance, and, paradoxically, antibiotics and notably penicillin can be responsible for the emergence of one of these. By preventing the premature death of patients with pneumococcal endocarditis, a hitherto almost uniformly fatal disorder, penicillin enables some of these persons to recover from their bacterial infection even though they may suffer in a number of instances rupture of the aortic valve as a result of bacterial damage prior to therapy. Such a sequence of events has been observed in the past decade in eight patients, and they comprise the subject of the present report. Before they are described, however, a brief review of knowledge relating to the clinical picture they present may be pertinent.

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Recognition of the association of pneumonia, endocarditis, and meningitis is not new. Perhaps the first to relate these lesions to one another was the Austrian pathologist, Heschl, who described, in 1862, autopsies upon five patients dying with this triad of abnormalities.[1] In 1881, the year pneumococcus was discovered, Osler wrote in a paper entitled "Infectious (So-Called Ulcerative) Endocarditis":

> Meningitis is a very rare complication of pneumonia and may occur apart from endocarditis; but in a case of inflammation of the lungs, particularly if the apex is involved (in three out of four such instances I found the upper part of the lung affected), the development of an irregular temperature with cerebral symptoms should suggest the possibility of endocardial mischief, with secondary meningeal inflammation.[2]

To the French physician, Netter, however, must go much of the credit for elucidating the pathogenesis of pneumococcal endocarditis. In 1886, he reviewed 82 cases of endocarditis associated with pneumonia, including two observed by himself.[3] He demonstrated the similarity of the organism isolated from endocardial vegetations to that recovered from the lung in seven fatal cases and grew pneumococcus from the blood of a patient shown subsequently to have endocarditis of the tricuspid valve. By traumatizing the aortic valve of the rabbit with a stylet passed down the carotid artery, he was able to produce experimental endocarditis in this animal following subsequent infection with pneumococcus. He pointed out the predilection of pneumococcus for localization upon the aortic valve whether normal or previously diseased and the relative frequency with which it attacks the valves of the right side of the heart. He was impressed also with the high incidence

of meningitis in those with this cardiac disorder.

In 1904, Preble reviewed again the subject of pneumococcal endocarditis, adding 50 cases to those studied earlier by Netter and emphasizing the clinical aspects of the disease.[4] He noted its more frequent occurrence in older persons, its variable duration, with death occurring on the average a month following onset, and its complication by meningitis in approximately three-fifths of the cases. One additional observation, made also by Netter, is noteworthy. In 20 of the patients, an afebrile interval was observed following the period of pneumonia and prior to the recrudescence of fever associated with endocarditis. In a temperature chart shown in Netter's paper,[3] defervescence occurred at the usual time of crisis in pneumococcal pneumonia, only to be followed in three to four days by a return of fever. The phenomenon points to the probable inefficacy of antibody as an aid to the eradication of infection of the endocardium, which view is supported by later evidence. Thomas and O'Hara described fatality following the administration of large amounts of specific antiserum to a patient with Type I pneumococcal endocarditis.[5] In this patient, fever and bacteremia recurred following the artificial induction of crisis with passive immunization and persisted despite repeated injections of antibody. Of interest also are the observations of Wadsworth and Sickles upon endocarditis in horses immunized with live pneumococcal vaccines.[6] Not only did these animals develop endocarditis at a time when circulating type-specific antibody was demonstrable, but in the course of continuing infection, the selective effect of capsular antibody upon the bacterial population of the infected animal led to the appearance, at times, of noncapsulated pneumococci in the circulation. Because natural recovery from pneumococcal infection is dependent almost wholly upon phagocytosis of the invading organisms by polymorphonuclear leukocytes, these observations point to a local failure of the phagocytic mechanism in endocardial infection. If this inference is a correct one, then recovery following treatment with other than a bactericidal agent will not be likely. The failure of the bacteriostatic sulfonamides to modify the uniformly fatal outcome in pneumococcal endocarditis is consistent with this view, and Heffron's statement in his monograph of 1939[7] that it is doubtful that an authenticated instance of recovery from the disease had ever been reported remained largely true until penicillin became available for the treatment of it.

From the foregoing discussion, it is evident that the association of pneumococcal endocarditis and meningitis has long been recognized and that until recently death from infection has been the outcome for those so afflicted. The introduction of a drug bactericidal for pneumococcus has modified significantly the clinical course of the syndrome, and, by making possible survival from infection, penicillin has allowed the recognition of a new group of patients with aortic insufficiency.

CASE 1.—The first patient of this series, a 46-year-old Negro man, was admitted because of his irrational mental state to Sydenham Hospital, in Baltimore, on Feb. 1, 1946. Four weeks previously he had developed pneumonia, for the treatment of which his physician had prescribed a sulfonamide. He had improved gradually until the day before hospitalization, when his temperature rose and he complained of a stiff neck. Twenty-four hours later he became delirious and was brought to the hospital.

Physical examination at the time of admission showed an acutely ill, delirious man with a temperature of 104.8 F. The classical signs of meningeal irritation were present. Evidence of pneumonia was not detected. The heart was of normal size, and the cardiac sounds were clear. Aside from a soft systolic murmur audible just to the left of the sternum, no auscultatory abnormalities were recorded. The pulse rate was 120, and the blood pressure, 148/90.

Examination of the spinal fluid confirmed promptly the clinical impression of meningitis, and pneumococcus Type XIV was grown both from the blood and from the spinal fluid. The serologic test for syphilis was positive in the blood but negative in the spinal fluid.

Treatment with sulfadiazine intravenously and with penicillin intravenously and intrathecally was instituted promptly, and over a period of 10 days

the patient's mental state improved gradually. His temperature returned to normal on the 18th hospital day, but his course was marked later by several episodes of fever and of pulmonary infiltration which, in retrospect, may have resulted from pulmonary infarction.

On March 28, the heart was noted for the first time to be enlarged, and an aortic diastolic murmur was heard along the left sternal border. Because the patient's serologic test for syphilis was persistently positive, he was thought to have syphilitic aortic insufficiency which had been overlooked at the time of admission, and he was transferred to The Johns Hopkins Hospital for further study. There the diagnosis of aortic insufficiency of syphilitic origin was also deemed likely, and the patient was discharged without evidence of cardiac failure on May 8.

He returned to The Johns Hopkins Hospital 18 days later complaining of swollen ankles and of nocturnal shortness of breath of a week's duration. Signs of cardiac failure were present. Digitalization by the oral route was begun, but the patient died suddenly and unexpectedly the night of admission to the hospital. The final clinical impression was syphilitic aortic insufficiency.

Autopsy performed four hours after death showed the aorta to be normal. The heart was enlarged but manifested none of the stigmata of treponemal infection. Instead, a perforation of the left cusp of the aortic valve (Fig. 1) 6 mm. in diameter was present which, on microscopic examination, showed at its margins remnants of a healing vegetation. The pathological diagnosis was healed bacterial endocarditis with perforation of an aortic cusp.

CASE 2.—Only one day after the death of the patient whose history has been recounted, a 65-year-old Negro man was admitted to the medical wards of The Johns Hopkins Hospital with meningitis and bacteremia caused by Pneumococcus Type XII and signs of aortic insufficiency. As a result of the preceding experience the clinical diagnosis of pneumococcal endocarditis was made, and, when the patient died two and a half months after his initial hospitalization, the clinical impression was confirmed at autopsy.

Since the time of the deaths of the two patients just described, six additional cases of pneumococcal endocarditis with rupture of the aortic valve have been recognized (Table). Among the total of eight patients, all but one were men, and all were over the age of 40. Seven were hospitalized with clinical and laboratory evidence of meningitis, and the eighth patient had a well-documented history of meningitis two months prior to the pneumococcal infection.

Fig. 1.—Photograph of the heart of Case 1, showing the perforation of a cusp of the aortic valve.

Clinical and Laboratory Data Pertaining to Eight Patients with Pneumococcal Endocarditis and Rupture of the Aortic Valve

Case	Age	Sex	Race	Blood Culture	C.S.F. Culture	S.T.S.	Detection of Aortic Insufficiency, Days After Admission	Duration of Life, Days After Detection of Aortic Insufficiency
1	47	M	N	Pne XIV	Pne XIV	+	55	60
2	65	M	N	Pne XII	Pne XII	−	On admn.	75
3	50	M	N	Pne XXII	Pne XXII	+	On admn.	41
4	43	F	N	Pne XII	Pos. smear	±	3	8
5	74	M	W	Pne XIV	Pne XIV	?	20	1
6	44	M	W	Pne VIII	Pne VIII	−	19	185
7	55	M	W	Pne XVIII	Pne XVIII	−	3	135+
8	40	M	N	Pne III	....	−	12	565+

during the course of which aortic insufficiency was recognized for the first time. Six of the eight patients had no evidence of cardiac disease when examined initially; but two, one of whom had late syphilis, had signs of aortic insufficiency when first seen. In those lacking the murmur of aortic insufficiency when hospitalized, it was detected first on the 3d to the 55th day following admission. It is not improbable, however, that its presence in some patients might have been noted earlier had it been sought more carefully.

All eight patients were treated with penicillin when hospitalized with meningitis, though in varying amounts and by different routes of administration. The dosage ranged from 240,000 to 60,000,000 units per day. Intrathecal therapy was employed in the treatment of three patients, and sulfonamides were administered concomitant with penicillin to four.

Case 8.—This patient had an unusual course. He was hospitalized elsewhere with purulent meningitis in October, 1954, and recovered after treatment with penicillin, though the causative organism was not isolated. No evidence of cardiac disease was noted at this time. Two months later, he was admitted to the medical wards with lobar pneumonia and bacteremia caused by Pneumococcus Type III, at which time his heart was again described as normal. He was treated with tetracycline for nine days, the last two of which he was afebrile. Three days following cessation of antibacterial therapy, an aortic diastolic murmur was heard, though the patient's temperature remained normal. He was given additional treatment with penicillin and remained free of signs of infection.

Development of altered circulatory dynamics after rupture of the aortic valve has been followed with recorded observations in one patient, Case 7.

Case 7.—The patient, a 55-year-old white man, was admitted to the hospital with pneumonia involving the right middle lobe and with meningitis caused by Pneumococcus Type XVIII. Three days after admission, a faint murmur of aortic insufficiency was heard for the first time. Five days later, recordings were made of the patient's ballistocardiogram, carotid pulse curve, and stethophonogram. The only abnormality detected was the presence of the aortic diastolic murmur (Fig. 2). One month later, little change from the initial tracings was evident, but four months after hospitalization, alterations in the ballistocardiogram, carotid pulse curve, and stethophonogram, all characteristic of aortic insufficiency, were noted. When last examined, the patient was in severe cardiac failure aggravated by multiple episodes of pulmonary infarction.

Death in the six fatal cases occurred from 1 day to 6 months after the signs of aortic insufficiency were first recognized and from 11 days to 7 months following initial hospitalization for pneumococcal infection. In all instances, the fatal outcome was preceded by myocardial failure. Two patients, Cases 7 and 8, were known to be alive 4 months and 20 months, respectively, after the development of aortic insufficiency, though the former was in severe cardiac failure.

Four of the patients who died were examined post mortem, and all showed evidence of healed bacterial endocarditis of the aortic valve, with rupture or perforation of a leaflet. Of the four, two had had

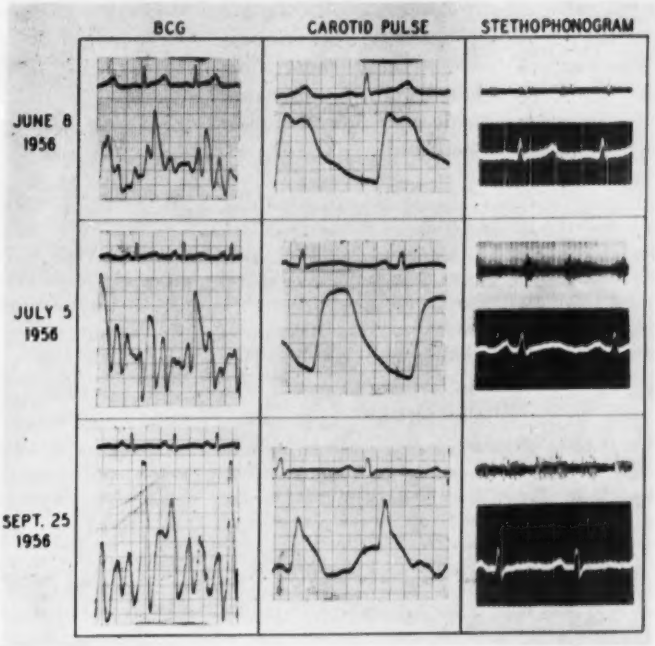

Fig. 2.—Serial ballistocardiograms, carotid pulse tracings, and stethophonograms recorded at Erb's point of Case 7. The tracings show the increasing intensity and duration of the aortic diastolic murmur, a progressive increase in the amplitude of the systolic complexes of the ballistocardiogram, and, in the latest record, a shortening of the time from onset to attainment of the peak systolic pressure in the carotid pulse wave, all characteristic findings of progressive aortic insufficiency. All ECG tracings for timing the cardiac cycle are Lead 2.

positive serologic tests for syphilis and two an aortic diastolic murmur at the time of hospitalization. The only patient with both these findings presented pathologic changes compatible with those of healed bacterial endocarditis superimposed upon a preexisting luetic lesion.

From the data reviewed, it appears that the syndrome of pneumococcal endocarditis, meningitis, and rupture of the aortic valve, while uncommon, is not rare, for it has been observed in approximately 20% of the patients with pneumococcal meningitis seen by me in the past decade. The presence of pneumococcal endocarditis may be anticipated in a quarter to a third of patients hospitalized with pneumococcal meningitis and will be detected perhaps more often if this association is borne in mind. Following adequate treatment with penicillin, survival from infection will result in most, but for those sustaining rupture of the aortic valve, the prognosis is grave, the majority dying of left ventricular failure within six months.

Only since the advent of penicillin has recovery from pneumococcal endocarditis been possible, and the minimal amount of this antibiotic requisite for cure is unknown. A recovery following treatment with less than 300,000 units of penicillin a day is included in this series, and in terms of present day usage, this is not a large amount of antibiotic. In patients with aortic insufficiency of uncertain origin, the possibility of healed pneumococcal endocarditis merits consideration along with other unusual causes of this lesion, and a history of pneumococcal infection should be sought.

Summary

A review of the history of pneumococcal endocarditis points to the probable failure of normal phagocytic mechanisms in endocardial infection and to the need for a bactericidal agent to effect cure of such infection. Treatment with penicillin enables survival from pneumococcal endocarditis but may fail to prevent rupture of the aortic valve as a sequel to valvular injury from infection prior to therapy. Patients surviving infection but sustaining rupture of the

aortic valve usually develop cardiac failure and have a poor prognosis. The frequent association of pneumococcal endocarditis and meningitis is noted, and the importance of examining patients with pneumococcal meningitis for evidence of endocardial lesions is stressed.

Dr. A. McGehee Harvey, Physician-in-Chief, and Dr. Arnold R. Rich, Pathologist-in-Chief, The Johns Hopkins Hospital, Baltimore, gave permission to include in this report clinical and pathological data relating to Cases 1, 2, and 3.

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Steroid Pseudorheumatism

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In five patients who have been on long-term adrenal steroid treatment we have observed a syndrome which superficially mimics rheumatoid arthritis. The symptoms of this syndrome, we believe, are often mistaken for increased activity of rheumatoid arthritis. An evaluation of the symptoms of this syndrome leads to the conclusion that it can be separated into a distinct clinical entity which in some way is the function of prolonged steroid treatment or of rapid withdrawal of steroids following a period of therapy. It is the purpose of this report to present a detailed description of each of five patients having this syndrome whom we have studied. We shall attempt to demonstrate from this clinical study that steroid pseudorheumatism is a clinical entity which mimics rheumatoid arthritis and the treatment of which is the gradual, but persistent, discontinuation of steroid therapy. We interpret these observations as a further warning against the indiscriminate or unnecessary use of steroid hormones which continue to reveal pharmacological actions threatening to the body economy that are still incompletely understood.

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Report of Cases

CASE 1.—A 43-year-old white man was admitted to the hospital with the complaints of generalized weakness, muscle cramps and tenderness, joint pain, and unusual mood changes. In December, 1947, the patient experienced his first attack of rheumatoid arthritis. He had migratory polyarthritis and developed deformities of the hands, elbows, knees, and ankles. Manifestations were aggravated by cold, dampness, and hard work. In 1953 the patient was hospitalized at another university hospital for a severe rheumatoid recrudescence involving primarily the knees. He was given a hydrocortisone injection in the left knee, with relief for seven days. At this time 6 gm. of uncoated acetylsalicylic acid per day was prescribed. However, the acetylsalicylic acid irritated his stomach, and he discontinued the medication. Then he was given a course of fever therapy without any improvement. At this time (August, 1953) he was given 100 mg. of cortisone per day and released from the hospital. He took this dosage continuously until admission to this hospital in January, 1956. For an indefinite period prior to admission, the patient noted that he was tired, fatigued easily, had muscle cramps, and had slight joint swelling. There were periods of marked depression, and it had become difficult for him to work. He stated that he had the feeling that he was constantly "losing ground." Six weeks prior to admission the patient ran out of cortisone, and the steroid therapy was abruptly stopped. Shortly thereafter he developed severe pain in the muscles and joints and extreme malaise. He resumed taking 100 mg. of cortisone several days later but could not suppress the muscle and joint symptoms entirely. Therefore, he came to this hosiptal for treatment.

Past history was significant in that the patient had increasing dyspnea which was the result of a progressive emphysema. Family history was significant in that one sibling has rheumatoid arthritis.

Physical examination revealed deformities in all extremities and moderate obstructive emphysema. Joint examination revealed generalized capsular thickening with small effusions in the right second, third, and fourth metacarpal-phalangeal joints and each ankle joint. There was a moderate flexion contracture of each elbow. The rest of the joints

had old destructive changes. Remarkably absent among the joint manifestations was tenderness, erythema, or heat. However, the most striking manifestations on physical examination was the apparent tenderness and soreness of the muscles of the extremities. Indeed, the patient assumed a "touch me not" attitude when the extremities were palpated, which led many observers to believe the complaints were out of proportion to the actual pain.

Laboratory Studies.—Urinalysis and white blood cell count were normal. Hemoglobin was 12.4 gm. per 100 cc. Cell indices indicated a mild normocytic, normochromic anemia. Erythrocyte sedimentation rate was 88 mm/hour, Wintrobe method. Direct eosinophil count was 111/cubic millimeter. L. E. clot test was negative. V. D. R. L. and Wassermann were negative. Serum uric acid, fasting blood sugar, and serum electrolytes were normal. No blood was found in the stool. ECG was normal. Roentgenogram of the chest showed pulmonary fibrosis and emphysema. Roentgenograms of all the joints revealed changes which were compatible with severe rheumatoid arthritis.

Hospital Course.—The patient was given acetylsalicylic acid, 4.9 gm/day. The cortisone was cut by decrements of 12.5 mg. every seven days. He was given moderate exercise and warm baths and was encouraged to walk around on the ward as much as he desired, but definite rest periods were enforced. When the cortisone was cut to 50 mg/day the decrements were decreased to 6.25 mg. every seventh day. When the cortisone dosage reached 25 mg/day, repository corticotropin injection (ACTH gel), 20 units, was given each morning. The corticotropin was continued for five to seven days after the cortisone was stopped and then was gradually tapered. After the patient was off all steroids, urinary 17-hydroxycorticoid output was measured and was found to be 4 mg/24 hours, Silber-Porter method. Initially, when the cortisone dosage was being cut, the synovial reaction increased, so that there was a greater effusion in the joints, but there was no increase in tenderness. However, when the cortisone dosage reached 50 mg/day the effusions gradually decreased, so that by the time that the cortisone was completely stopped there was much less effusion than originally had been present. During the reduction program the white blood cell count remained within normal limits. The sedimentation rate remained at about 90 mm/hour, Wintrobe method, until approximately one-half way through the reduction schedule, when it gradually fell to 50 mm/hour, Wintrobe method, at which level it remained. Upon admission the patient had used full arm crutches but gradually started using Canadian crutches and then no cruthces at all. Orthopedic shoes with a metatarsal bar were obtained for the patient. He was discharged on a regimen of enteric-coated acetylsalicylic acid, 900 mg. five times per day, appropriate rest periods, and physical therapy. At present he has been home working at his job for two months. The manifestations which prompted his hospitalization have completely disappeared.

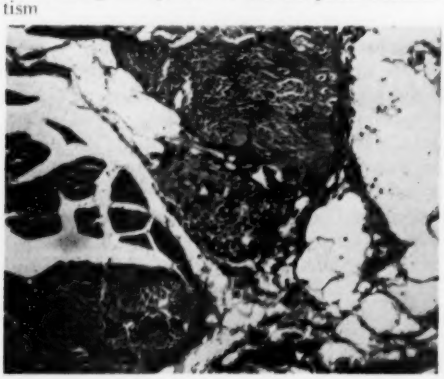
Case 2.—This 37-year-old white male accountant was admitted to the hospital with the complaints of muscle and joint pain, swelling of the face and supraclavicular areas, and excessive irritability. In 1943-1944 he developed rheumatoid arthritis. He was treated with fever therapy, neostigmine (Prostigmin) chloride, and acetylsalicylic acid. From 1944-1950 he had many recrudescences of rheumatoid arthritis, with the development of little joint deformity. In 1950 the rheumatoid activity continued, and he began to develop deformity of the knees and ankles. Consequently, in 1951 he was given cortisone in a dosage of 100 mg/day. In 1953 the arthritis extended to the arms. He was seen for the first time at this hospital in 1953 and was found to have an acute episode of rheumatoid arthritis which was controlled by 100 mg. of cortisone per day. At this time atrophy was noted in the muscles of the extremities. He complained of numbness in the lateral part of the left foot and over the left lateral malleolus. Sensation to pin-prick was diminished, and the diagnosis of cortisone neuritis was made. He was given large oral doses of vitamins B and C for four weeks without improvement in sensation. Cortisone, 100 mg/day, was continued until June, 1955, when he was given 15 mg. of prednisone per day plus miltivitamins and acetylsalicylic acid, 900 mg. t. i. d. An attempt to cut the dosage of steroid was made both in 1953 and 1955, but each time it was cut the patient complained of aching and pain in the joints and muscles, and the reduction schedule was discontinued. Although he had been on a low-salt diet, the patient stated that for two weeks prior to admission he began to gain a large amount of weight. The weight gain was in excess of that attributable to the supraclavicular fat pad and the puffiness of the face, which had gradually increased over a period of four months. For three to four months prior to admission he had noticed muscle cramps, tenderness of the joints, and a feeling of fatigue. Also, he was much more irritable than usual and had difficulty in remembering details. The patient began to drink heavily, which was unusual for him. His wife stated that he was irresponsible during the four months prior to admission. Although previously he held a job as an accountant for an automobile firm, he now was irregular in his hours and could not be counted upon to fulfill his work schedule. Past history

and system review was noncontributory. There is no allergic or arthritic history in the family.

Physical Examination.—In general appearance the patient was a well-developed, well-nourished white man who had limb deformities and muscle atrophy. He was well oriented but complained of generalized aching. Moon facies, ruddiness of the face, full supraclavicular areas, and a suggestion of a buffalo hump were present. The blood pressure and pulse were normal. There were no other abnormal physical findings save for those in the extremity and neurological examinations. Joint examination revealed generalized capsular thickening, with moderate flexion contractures of the elbows and knees. There was a small effusion in the right knee joint. The right ankle joint was tender. The muscles of the extremities were extremely tender to palpation. The picture was that of a low-grade rheumatoid arthritis with disproportionate pain and tenderness of the muscles. Neurological examination revealed decreased pinprick sensation over the lateral part of the left foot and left medial malleolus.

Laboratory Studies.—Urinalysis, white blood cell count, and hemoglobin value were normal. Erythrocyte sedimentation rate was 58 mm/hour, Wintrobe method. V. D. R. L. was negative. C-reactive protein was negative. Serum uric acid, electrolytes, fasting blood sugar, and liver function tests, were normal. Repeated L. E. clot tests were negative. No blood was found in the stool. Roentgenogram of the chest revealed old fibrocalcific disease of the right upper lobe. Roentgenograms of all of the joints revealed varying amounts of destructive changes and osteoporosis compatible with rheumatoid arthritis. Gastrointestinal series and ECG were normal. Muscle biopsy of the right deltoid muscle revealed atrophied muscle and a necrotizing arteritis (Figure). This process involved primarily the small blood vessels, and no involvement or nodule formation in medium-sized blood vessels was observed.

Inflammatory reaction about a small blood vessel in the section of muscle tissue taken from a patient during an episode of steroid pseudorheumatism



Rotstein—Good

Hospital Course.—The patient was weaned from prednisone with decrements of 2.5 mg. every seven days. He was placed on a regimen of acetylsalicylic acid, 900 mg. five times a day; thiamine hydrochloride, 100 mg/day; warm tub baths; exercise as tolerated; enforced periods of bed rest, and a low-salt diet. He lost 15 lb. of weight within two and one-half weeks. With each decrement of prednisone there was a period of two to three days wherein the patient felt tired and irritable, had memory gaps, and could not think clearly. During these periods he slept a good deal. However, when he felt better he was up and about and continued his duties. As the prednisone dose reached levels of 7.5 mg., these periods of ill-being decreased. When 5 mg/day of prednisone was reached, he was given repository corticotropin injection, 20 units, in the morning. At this time the decrements of prednisone were lowered to 1 mg. every seven to ten days. The patient ceased having periods of ill-being when the prednisone was cut to 2.5 mg/day. The prednisone was finally stopped and the corticotropin tapered and then discontinued. Shortly thereafter, urinary 17-hydroxycorticoid excretion was 4.6 mg/24 hours, Silber-Porter method. During the reduction program the neuritis of the left foot slowly disappeared, and at the present time sensation is almost normal. Throughout the reduction period the erythrocyte sedimentation rate and white blood cell count remained relatively stable. A course of gold therapy was initiated after discontinuation of the steroids in order to build up a gold depot in an attempt to ameliorate further rheumatoid recrudescences. The patient has returned home on a regimen of acetylsalicylic acid, 900 mg. five times per day, and maintenance gold, 50 mg. every month. The pain and tenderness of the muscles and bones have completely disappeared. He is getting along well and working at his former occupation.

Case 3.—This 67-year-old retired white male grocery clerk was admitted to the hospital with the complaints of generalized aching, tenderness of the chest muscles, and inability to draw a deep breath. In 1951 the patient developed pain in both acromioclavicular and sternoclavicular joints. Shortly thereafter this was followed by migratory joint erythema, swelling, and pain in all metacarpophalangeal and interphalangeal joints. The patient was given 75 mg. of cortisone and 3 gm. of acetylsalicylic acid per day for six months with good relief. He had several mild rheumatoid recrudescences in 1953 and early 1954; these were suppressed by 3-4 gm. of acetylsalicylic acid per day during the periods of acute disease. In mid-1954 the patient experienced a severe recrudes-

cence of migratory polyarthritis which responded poorly to a short course of high doses of acetylsalicylic acid. He was given hydrocortisone, 50 mg/day, and then switched to prednisone, 15 mg/day, on which medication he had remained until this admission. For approximately six months prior to admission the patient noted gradually increasing fullness of the face and supraclavicular areas, weight gain, and, most troublesome of all, generalized aching in the joints and muscles with a marked sensation of burning, pain, and tenderness in the intercostal muscles. He was afraid to draw a deep breath, as this would increase the thoracic muscle pain. Past history and family history are noncontributory.

Physical Examination.—The patient exhibited a moon facies, with increased supraclavicular fat pads. There were slight emphysematous changes in the chest. The patient complained of tenderness when the muscles of the extremities were palpated. Joint examination revealed slight bilateral flexion contractures of the elbows and knees, with thickened capsules of the shoulder, elbow, wrist, knee, and ankle joints. Moderate limitation of motion of the shoulder, elbow, and knee joints was present. In no joint was there effusion, heat, or erythema. On palpation of the joints the patient complained of slight tenderness, which was much less severe than the muscle tenderness already mentioned.

Laboratory Studies.—Urinalysis and hemogram were normal. Erythrocyte sedimentation rate was 60 mm/hour, Wintrobe method. C-reactive protein and L. E. clot test were negative. Serum electrolytes, fasting blood sugar, and uric acid were normal. V. D. R. L. was negative. Total proteins and A/G ratio were normal. No blood was found in the stool. ECG was abnormal, with nonspecific ST-T wave changes. Timed vital capacity was 60% of normal. Roentgenograms of the chest revealed bilateral pulmonary fibrosis and changes compatible with emphysema. Roentgenographic changes of the joints revealed findings consistent with old rheumatoid arthritis, involving all of the joints except the hips. Considerable osteoporosis of the humeri and hand bones was noted.

Hospital Course.—The patient was given acetylsalicylic acid, 900 mg. q. 4 h., physiotherapy, and rest periods. The prednisone was cut by decrements of 2.5 mg. every 7-10 days. The patient complained bitterly about increased symptoms, particularly of difficulty in breathing, which, upon careful questioning, appeared almost entirely to be related to periodic spasms or cramps of the intercostal muscles and constant "burning" and aching of these muscles. He resisted any exercise during the first two weeks of the reduction program. The dosage decrements were reduced to 1 mg. every seven days, and gradually the patient became less truculent and more cooperative. When the dosage of prednisone reached approximately 8 mg/day the muscle symptoms gradually abated. A course of repository corticotropin injection, 20 units every morning, was started when the prednisone dosage reached 5.0 mg/day and was slowly tapered when the prednisone had been entirely discontinued. Three weeks after the steroids were discontinued the patient developed a severe upper respiratory infection. He complained of joint and muscle pain, and on examination there was effusion, heat, and tenderness of the wrists and the metacarpophalangeal and interphalangeal joints. The muscles of the arms were tender, but less so than at the beginning of the prednisone withdrawal program. The patient was treated with 600,000 units of procaine penicillin b. i. d. and 2.5 mg. of prednisone each morning for the duration of the cold. Then the prednisone was slowly tapered. Joint and muscle symptoms completely abated. During the reduction program the erythrocyte sedimentation rate went up to 80 mm/hour, Wintrobe method, but at the end of the program (prior to the upper respiratory infection) it was 52 mm/hour. The white blood cell count remained stable. At the present time the patient is on a regimen of 900 mg. of acetylsalicylic acid five times per day and physiotherapy. He is up and about and states that he feels better than at any time since 1951.

CASE 4.—This 62-year-old white male post office worker was admitted to the hospital with the complaints of swelling, redness and tenderness of the ankles, pretibial edema, pain in the muscles of the arms, and a feeling of "being sick all over." The patient first developed migratory polyarthritis in 1941. He was treated with acetylsalicylic acid and a course of gold injections with good results. From 1941-1952 the patient experienced a rheumatoid recrudescence approximately every two years and was treated with a course of gold therapy with resultant remissions. Acetylsalicylic acid was taken intermittently. In 1954 he was given hydrocortisone, 50 mg/day, which did not control his symptoms. He was admitted to this hospital for the first time in 1955 and found to have acute rheumatoid activity in all joints save the hips. Serum uric acid was 7.7 mg. per 100 cc. A diagnosis of mixed arthritis (gout and rheumatoid arthritis) was made. The patient was treated with prednisone, 15 mg/day; colchicine, 1 mg/day, and probenecid (Benemid), 2 gm/day. The serum uric acid level dropped to 4.3 mg. per 100 cc. Gradually all joint symptoms cleared, and the patient was discharged on a regimen of 10 mg. of prednisone and 2 gm. of probenecid per day. The patient continued taking these medications and felt well until November, 1955, when he developed stiffness,

swelling, and erythema of the ankles, with 2+ pretibial edema. Although the patient maintained a low-sodium diet, the edema progressed. In January, 1956, the patient developed muscle pain and mood fluctuations, which were unusual for him. In February, 1956, there was increased pain in the ankle and knee joints, tenderness of the muscles of the extremities, and moderately severe exertional dyspnea. The patient was admitted to this hospital.

Physical examination revealed a well-developed white man with moon facies, who complained of aching and tenderness of the muscles of the extremities. Chest examination revealed bilateral basilar rales. The blood pressure was slightly elevated; the pulse was 90, and there was mid-diastolic gallop rhythm. The heart was not enlarged. He had moderate enlargement of the liver and 4+ pitting edema of the legs. Examination of the joints revealed capsular thickening of the elbows, wrists, and hand joints, but no signs of current rheumatoid activity were present. The leg muscles were atrophied, and there was tenderness, swelling, redness, and heat of the knee and ankle joints. A small nodule was present in the subcutaneous tissue over the left radius. No tophi were present. The muscles of the extremities were moderately tender.

Laboratory Studies.—Hemogram and urinalysis were normal. Erythrocyte sedimentation rate was 62 mm/hour, Wintrobe method, and C-reactive protein was 1+. Serum uric acid and urine uric acid clearance were normal. Total proteins and A/G ratio, fasting blood sugar, and serum electrolytes were normal. L. E. clot test was negative. ECG was abnormal, with nonspecific ST-T wave changes. Roentgenogram of the chest revealed the heart to be of normal size, but the lungs showed mild congestion. Roentgenograms of the joints revealed osteoporosis and hypertrophic changes consistent with degenerative osteoarthritis superimposed upon rheumatoid arthritis. Spine roentgenograms revealed generalized osteoporosis. Excision and histological section of the subcutaneous nodule of the left forearm revealed a characteristic rheumatoid nodule.

Hospital Course.—The patient was placed on a rigid cardiac regimen for the cardiac decompensation. It was believed that the patient was experiencing a rheumatoid recrudescence superimposed upon mild steroid pseudorheumatism. Therefore prednisone, 15 mg/day, was continued, and acetylsalicylic acid, 900 mg. q. 4 h., was prescribed along with rest and physiotherapy. Gradually the joint symptoms remitted, but the muscle tenderness and mood fluctuations continued. Following abatement of active synovitis the prednisone was decreased 1 mg. every seven days. However, whenever the steroid level fell below 12 mg/day the patient complained so bitterly about increased muscle and joint pain, without proportionate objective findings, and had such severe mood fluctuations that the prednisone was increased to 15 mg/day. Finally, a course of gold therapy was instituted in addition to the prednisone and acetylsalicylic acid. When a depot of 300 mg. of gold was built up the prednisone decrements were started, 1 mg. every 10 days. Exacerbations of the muscle and joint pain, with mild acute synovitis of the ankle joints, occurred at prednisone dosages of 10 and 7 mg/day. However, at neither time was the steroid increased; rather, the decrements were halted for 15 days and then continued. During the reduction program the erythrocyte sedimentation rate varied between 60 and 88 mm/hours without relation to symptoms. The white blood cell count rose slightly at the beginning of the program but then returned to normal. At the present time the patient is maintained on 1 mg. of prednisone per day and 900 mg. of acetylsalicylic acid five times per day. He has a depot of 600 mg. of gold and is maintained on 50 mg. of gold salt per month. There are no signs of cardiac decompensation or emotional instability. Muscle and joint pain have disappeared completely, and currently there are no signs of rheumatoid activity. Prednisone will be discontinued entirely in a short time.

CASE 5.—A 15-year-old boy first became ill in April, 1954. At that time he developed a severe sore throat, followed in one week by occurrence of fever, leukocytosis, migratory polyarthritis, and abdominal pain and tenderness. A diagnosis of rheumatic fever was made, and he was hospitalized.

Physical examination revealed evidence of marked cardiac enlargement, cardiac failure, pericardial friction rub, systolic and diastolic heart murmurs, and evidence of arthritis in knees and ankles. Laboratory examination revealed the sedimentation rate to be 98 mm/hour (Westergren); C-reactive protein, 5+, and mucoprotein, 18.5 mg. per 100 cc. of mucoprotein tyrosine. The antistreptolysin titer was 1000 Todd units/cubic centimeter. Initially he had migratory polyarthritis involving the knees, ankles, shoulders, wrists, and elbows. Blood cultures and muscle biopsies were negative, as were bone marrow studies for L. E. cells. Because of the overwhelming rheumatic disease the patient was given corticotropin, 150 mg/day. During a two-month course of treatment the toxicity and carditis gradually abated, but the laboratory signs of rheumatic activity persisted, so the dosage of corticotropin was increased to 200 mg/day. Over a one-month period the sedimentation rate came down to normal, C-reactive protein disappeared from the serum, and the mucoprotein began to drop. On the large dosage of

corticotropin the patient developed Cushing's syndrome, and the corticotropin treatment was gradually tapered and discontinued over a two-month period. Within three weeks following withdrawal of corticotropin, a rheumatic rebound occurred which was manifest as fever, abdominal pain, marked elevation of erythrocyte sedimentation rate, appearance of C-reactive protein, and increase in mucoprotein concentration in the serum. Although no further steroid therapy was used at this time, the sedimentation rate spontaneously returned to normal, the C-reactive protein disappeared from the serum, and the mucoprotein returned toward normal. There was no evidence of residual carditis on the discharge examination, and only a soft systolic murmur was heard. Three months later, in spite of continuing prophylaxis with penicillin, the patient developed a sore throat followed in a few days by pain in the knees and wrists and elevation of the sedimentation rate. It was the opinion of the attending physicians at this time that the recurrence of symptomatology was due to exacerbation of rheumatic activity rather than a new attack of rheumatic fever, largely because no streptococci could be isolated from the throat, the antistreptolysin titer did not increase, and the mucoproteins had never returned completely to normal following the prior attack of rheumatic fever. He was again treated with corticotropin in a dosage of 200 mg. over a three-week period, which resulted in subsidence of arthritis, drop in sedimentation rate, and disappearance of fever. He was then switched over to cortisone, 150 mg/day, which was continued over a period of one month. While taking cortisone he developed marked Cushing's syndrome, with typical facies, acne, buffalo hump, supraclavicular deposition of fat, and purpura. Because of continued elevation of the sedimentation rate, the cortisone was discontinued, and he was again treated with corticotropin over a two-month period. Toward the end of this period of therapy he developed pain and tenderness of the bones, muscles, tendons, and joints, especially in the lower extremities, and considerable atrophy of the muscles of the lower extremities. He became irritable and depressed. Because of the continuing and extending symptoms and because, in spite of negative muscle biopsy, several consultants now thought the patient was suffering from periarteritis nodosa he was started on prednisone by mouth in a dosage of 80 mg/day. Although the symptoms improved slightly on this therapy, the improvement was short-lived, and again muscle pain and tenderness and irritability developed; elevation of the sedimentation rate and joint and tendon pain recurred. The dosage of prednisone was increased to 100 mg/day, which was administered over an 11-day period and then increased to 120 mg/day. The latter dosage was given for one month. Again, although there was some improvement with each dosage increment, the beneficial effect would quickly be lost, and severe symptoms referable to the muscles and extremities would recur. While on this large dose of prednisone the patient developed pain, tenderness, and burning sensation of the intercostal muscles, more marked on the left than on the right. This symptom was so severe that it made breathing difficult and necessitated use of narcotics to control the virtually unbearable pain. In addition, the patient complained of being sore all over. He was markedly irritable and severely depressed. He had tingling and burning sensations in his feet and sensation to heat, cold, and pain in the left foot became markedly diminished. The manifestations of Cushing's syndrome became extremely marked. The possibility of steroid pseudorheumatism was considered, the prednisone was discontinued, and he was again given corticotropin, in a dosage of 150 mg/day. Gradually the dosage of hormone was reduced, and after two months he was switched to hydrocortisone, 100 mg/day by mouth. A steady program of gradual reduction of the hormone dosage, approximately 2-3 mg/week, has resulted in gradual disappearance of the peripheral neuritis, muscle pain, tenderness, and burning sensation of the muscles. With each decrement of hormonal dosage, however, temporarly periods of joint pain, tenderness, aching of limbs, and occasionally muscle pain and tenderness occurred. After a few days on the new dosage, clinical improvement occurred, and physical rehabilitation could proceed as before the decrement was instituted. At the present time the patient is being rapidly rehabilitated. He is now given only 30 mg. of hydrocortisone per day, is up and about much of the time, is in good spirits, and has lost most of his Cushingoid features. The symptoms of muscle and bone pain, peripheral neuritis, and the burning sensations have completely disappeared.

Comment

The syndrome attributable to chronic overdosage with adrenal steroids occurring in patients with rheumatoid arthritis was first described by Slocumb, in two papers in 1952 and 1953.[1,2] Hench and Ward[3] discussed the occurrence of pseudorheumatoid symptoms in these patients in 1954. The syndrome has been seen almost exclusively during steroid treatment of rheumatoid arthritis. Although the reason for this is not clear, it seems likely from our

observations that this may be a function of the prolonged use of cortisone in these patients. One of our cases occurred in a child with rheumatic fever who had been given large doses of steroids for a considerable length of time in an effort to suppress severe cardiac disease. Recently the same syndrome has been observed by T. Good[4] in 7 of 10 normal human volunteers following rapid withdrawal of hormone after the administration of moderate doses of prednisolone for relatively short periods of time.

Sixty-six to seventy-five per cent of the patients who are given therapeutic doses of steroids develop some symptoms simulating Cushing's syndrome.[5-12] Often the steroid is continued despite these toxic effects when it is believed that the therapeutic efficacy outweighs the danger of overdosage. In many instances this course must be followed. However, from our observations and those of others [1,3] it would appear that a significant number of patients given steroids who exhibit Cushing symptoms and continue to receive heavy doses of steroids will manifest at some later date symptoms of steroid pseudorheumatism. According to Slocumb [1,2] the syndrome may develop in postmenopausal women who receive over 37.5 mg. of cortisone per day for over 30 days. In men and premenopausal women doses of 75 mg. of cortisone per day for over 50 days have been associated with the syndrome. Equivalent doses of hydrocortisone and the newer analogues may produce the same symptoms.[13,14]

Steroid pseudorheumatism manifests itself as a syndrome featured by periods of restlessness; emotional lability; asthenia; fatigue; muscle, bone, joint, and tendon pain, and memory deficit. In some instances the symptoms appear to be generalized and no area of the body can be palpated without the patient's inordinate objections. In others, specific areas, i. e., the intercostal muscles or the muscles of the extremities, may be exceedingly troublesome. Often the patient's complaints seem to be disproportionate to the objective findings. In some instances the muscles and bones hurt equally no matter where or how firmly they are palpated. The joints are not very tender, less so than the muscles, and they show surprisingly little swelling, erythema, or heat. At the height of symptoms the patient may complain of pain, cramps, and a burning sensation of the muscles. In our experience this manifestation may be very severe and is prone to involve the intercostal muscles. A peripheral neuritic component has been noted in our cases and was described in several of Slocumb's patients.[2] The neuritis consists of numbness, "burning," paresthesias, and loss of pin-prick sensation. In all of the patients suffering from steroid pseudorheumatism we, and others,[2,3] have noted mental irritability and irresponsibility. Concomitantly, there may be temporary memory deficits for recent and past events. An hour or two of rest will often rejuvenate the patient so that he is able to resume his daily activities for a short period of time. If steroid is given, the symptoms of pseudorheumatism abate only to return as the steroid is metabolized. For the patient with steroid pseudorheumatism the adrenal hormones seem to behave like narcotics to the addict.

So like the manifestations of rheumatoid arthritis are the symptoms of steroid pseudorheumatism that the sophisticated rheumatoid patient may complain to the physician that he is experiencing a rheumatoid "flare" on a dosage of hormone that was previously capable of suppressing all manifestations of arthritis. If the physician does not question and examine the patient thoroughly, he may be led to give more steroid to suppress a supposed rheumatoid recrudescence, only to have the patient experience another "flare" two weeks to a month later at the new dosage and so on with each increment until large amounts of steroid are being given.

If the manifestations of steroid pseudorheumatism are compared critically to the manifestations of rheumatoid arthritis, dis-

tinct differences become obvious. In rheumatoid arthritis the predominant symptoms are those of synovitis and inflammation of the articular and periarticular tissues; in pseudorheumatism the muscles and bones are the sites of predominant pain and are disproportionately tender. In the pseudorheumatoid patient periods of emotional lability, restlessness, and fatigue alternate with periods of well-being which follow an hour or two of test. In the true rheumatoid patient no such rapid fluctuation in symptoms occurs. Mentally the patient may be depressed and lack motivation during periods of rheumatoid recrudescence; however, memory deficit and irresponsibility are not prominent as they are during an attack of steroid pseudorheumatism. Exercise, heat, and physical therapy bring about improvement in the patient with rheumatoid symptoms, whereas in steroid pseudorheumatism these measures tend to aggravate the condition and the complaints increase. In both a rheumatoid recrudescence and steroid pseudorheumatism increased steroid dosage will alleviate symptoms. However, in a month or so on the increased dosage the patient with steroid pseudorheumatism will have a recurrence of symptoms, often in an exaggerated form. Although increased steroids decrease the symptoms, larger doses subsequently will be required. If the syndrome is not recognized, a vicious cycle of recurrent symptoms with increasing steroid dosage may be entered.

Scattered reports of the transformation of the more benign forms of mesenchymal disease, rheumatoid arthritis, and scleroderma into more malignant forms, such as lupus erythematosus or polyarteritis nodosa, during the course of prolonged treatment with large doses of cortisone have appeared.[6,15] In a recent provocative study Kemper [16] reviewed 52 autopsies of patients with rheumatoid arthritis, 14 of whom had received cortisone or corticotropin prior to death. Of these 14 patients, 3 had symptoms of steroid pseudorheumatism prior to death and 1 other had received heavy doses of cortisone for 32 days prior to death. The tissues of these four patients (28.9% of those given steroids and 7.7% of the total series) revealed extensive lesions of necrotizing arteritis, such as those characteristic of periarteritis nodosa. No rheumatoid patient not treated with steroids had these lesions. As necrotizing arteritis does not occur with any greater frequency in patients with rheumatoid arthritis than in normals, the author concludes that these lesions represent a significant effect of steroids on patients with rheumatoid arthritis. In one of our patients in whom a muscle biopsy was done, this same lesion was encountered (Figure). It seems possible to us that the syndrome of steroid pseudorheumatism is the clinical reflection of this pathological process.

The physician using steroid therapy must be aware of the syndrome of pseudorheumatism in order to employ hormonal therapy rationally. If steroid pseudorheumatism is encountered, the aim of treatment is gradual weaning from steroids and not an increase in hormonal dosage, even though the latter may temporarily relieve the clinical disease. Each patient represents an individual problem, and treatment must be adjusted to his needs. In some instances dosage increments to relieve symptoms may be temporarily expedient, but as soon as possible a program of dosage reduction should be instituted. The dosage should be reduced in small decrements at 7-10 day intervals. The decrements should not exceed 6.25-12 mg. for cortisone, 2.5-5.0 mg. for hydrocortisone; and 1.0-2.5 mg. for the newer analogues. In some instances even slower reduction of dosage is necessary. Supportive measures play an important part in the reduction program. Increased periods of rest are helpful, and physical therapy and exercise should be employed with caution. The patient should not be pushed beyond his tolerance. Encouragement and reassurance are very helpful. Salicylates, in sizeable quantities, are helpful, for the drug will allay much of the discomfort of withdrawal

and often is the main medicament used in subsequent months. Corticotropin in small doses may be used to stimulate endogenous production of corticoids while the steroid is being cut. The efficacy of corticotropin used in this manner is controversial. A tranquilizing agent may be used to ameliorate the mood fluctuation. Since rauwolfia has many undesirable side-effects and may compound certain side-effects of the steroid, such as increasing ulcerogenic tendencies and abnormal psychic manifestations, chlorpromazine and meprobamate would appear to be the tranquilizers of choice. However, the physiological site of action of meprobamate is as yet unknown, and its application in these patients must be considered to be investigational.

With the rapid discontinuation of hormone after short-term steroid treatment or even with the most gradual reduction of hormone dosage following prolonged treatment, symptoms referable to the joints and muscles may be manifest. The patient may complain of stiffness, pain, aching, and soreness; there may be fatigue and psychic instability. That these manifestations do not represent recurrence of the symptoms of the disease originally treated is indicated by the nature of the manifestations and by the recent observations of T. Good[4] that the same manifestations may occur in normal human volunteers following withdrawal of hormone even after short-term therapy.

When these symptoms occur it would seem wise to reassure the patient rather than increase his hormone dosage. Within a few days after beginning reduction in the dosage there should be release from the feeling of restlessness, and the patient will be able to think more clearly. The symptoms of aching and soreness gradually remit. As the dosage is lowered, the sedimentation rate may rise, but in rheumatoid patients it usually is not above pretreatment levels. Also, in some cases, a transitory increase even in synovial reaction will occur which later disappears as the steroid dosage is decreased. If there is additional stress at any time, such as respiratory infection, small increments of steroids may be given to tide the patient over the stress period; then the reduction regimen should be reinstituted. Of a more serious nature is the panmesenchymal reaction which may occur while the patient is being weaned from steroids. This is more apt to develop if the decrements are too large. If the patient has a severe reaction, all of the toxic stigmata of an acute episode of mesenchymal disease may be present.[2] There may be high fever, a great increase in the sedimentation rate, albuminuria, hematuria, pericarditis, pleurisy, pulmonary consolidation, thrombophlebitis, peripheral neuritis, iritis, and skin ulcers. L. E. cells may appear in the blood and bone marrow, and the Wassermann may become positive. There even may be tissue evidence of periarteritis. One or more of these symptoms appeared in 15 patients suffering from steroid pseudorheumatism whom Slocumb weaned from cortisone and in 21% of the patients under Freyberg's care.[1,2,17] Severe vascular, dermal, and connective tissue reactions have recently been reported following the discontinuation of prednisone therapy after prolonged treatment with large doses of this hormone.[18] Even though the reactions to withdrawal are severe, discontinuation of therapy may be and doubtless should be achieved by the very gradual reduction of hormone dosage.

Since no metabolic studies have been done, little is known of the mechanisms involved in steroid pseudorheumatism. However, some data have accumulated in the study of laboratory animals which indicate that cortisone treatment may enchance susceptibility of blood vessels to damage by macromolecular endotoxins like that responsible for the hemorrhagic necrosis characteristic of the Shwartzman reaction.[19-23] On the basis of these studies, Thomas[15] warned of the possible danger of producing subtle forms of vascular disease in man by long-term steroid treatment. It is possible that similar mechanisms are involved in

the experimental vascular diseases produced in the animals and the development of pseudorheumatism. This possibility seems particularly enticing in light of Kemper's thesis in which it was demonstrated that necrotizing vascular lesions occurred frequently in rheumatoid patients receiving cortisone. Perhaps, however, other effects on the integrity of the blood vessels, the reticuloendothelial system, or the protein and lipid-vascular relationships are responsible for this clinical expression of steroid toxicity. Only future investigation will provide understanding of the physiological mechanisms responsible for this syndrome.

The observation that disturbances such as those described herein occur in patients on prolonged steroid therapy serves to emphasize that the effects of steroid hormones are still poorly understood. In view of this consideration it remains our contention that these hormones should be reserved for clinical circumstances in which there is a commanding indication for their use. If steroid pseudorheumatism does occur, it must be recognized as a delicate clinical problem which can only be resolved by the decrease and eventual discontinuation of steroid therapy.

Summary

Five patients given prolonged adrenal steroid therapy having a syndrome which mimics rheumatoid arthritis and responds to discontinuation of hormone therapy are presented. A comparison of the manifestations of steroid pseudorheumatism and those of rheumatoid arthritis is made. The relationship of these observations to those presented by others is discussed, and a method of treatment of this disease is outlined. The implications of these observations on the indications for prolonged steroid therapy is considered.

Drs. Paul Bilka and Leslie Zieve gave encouragement and advice during the observation of these patients and the preparation of this paper.

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Serum Transaminase as a Diagnostic Aid

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Glutamic oxaloacetic transaminase, an enzyme which catalyzes the reversible transamination reaction by which glutamate and oxaloacetate interact to form aspartate and α-ketoglutarate, is present in high concentration in a number of animal tissues, but most notably in heart, liver, kidney, muscle, and brain.[1]

The serum or plasma level of glutamic oxaloacetic transaminase,* henceforth referred to as transaminase in this report, has recently come into prominence as a diagnostic aid in clinical medicine.[2-11] Following the initial observations by Karmen, Wróblewski and LaDue that all normal human sera contain transaminase activity and the development by Karmen of a simple technique for the quantitative assay of serum transaminase,[3] LaDue and his associates demonstrated that acute cardiac, hepatic, and skeletal muscle necrosis in man was associated with a significant rise in the level of serum transaminase activity.[2,4,5] These initial observations have been confirmed both in man[7-11] and under experimental conditions in animals,[12-15] where it also has been demonstrated that infarctions produced by ligation of the pulmonary, renal, splenic, and mesenteric arteries may produce elevated serum transaminase levels. In addition, elevation of serum transaminase activity has been frequently noted in patients with obstructive jaundice (without evidence of hepatic necrosis), suggesting that bile may represent an excretory pathway for the transaminase enzyme.[9]

Because of the increasing interest in assays of serum transaminase as a clinical diagnostic aid, it is the purpose of this report to present our observations on 701 patients with a variety of diseases † and to review the current status of the transaminase assay.

Methods

Serum transaminase activity is most commonly assayed by the method of Karmen,[2,3] which couples the transamination reaction with the oxidation of DPN in the presence of an excess of malic dehydrogenase.‡ The rate of disappearance of absorption at 340mμ (which is a measure of the oxidation of DPN) reflects the transaminase concentration and can readily be quantitated in terms of transaminase units. One transaminase unit has been defined by Karmen as that amount of enzyme which will cause a unit drop in optical density per minute under the conditions of the test. In our studies, the Karmen assay was simplified by not employing any blank § and by the use of 0.2 ml. of serum as a routine. In the presence of abnormally high activities, the serum was diluted as indicated. Assays on spinal fluid were carried out in an identical manner. Previous studies have shown that (*a*) assays on plasma specimens obtained with oxalate, citrate, or heparin as anticoagulants are similar to serum obtained from the same blood; (*b*) the enzyme in serum is quite stable at room temperature for periods up to four days, and (*c*) the enzyme in serum, when refrigerated, is stable for periods of one to two weeks.[8] Hemolysis, significantly alters the transaminase assay and may be a source of serious error.[7] Although platelets also contain transaminase,[16] it remains to be determined whether variations in platelet numbers will significantly alter the assay. Transaminase in serum appears to be fully acti-

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* Referred to by others as SGOT and serum aminopherase.

† The observations on the first 400 of these patients have been previously reported.[9]

‡ Obtained for our studies from the Sigma Chemical Co., St. Louis.

§ As suggested to us by Dr. Karmen.

vated, since the addition of excess coenzyme, pyridoxal phosphate, does not change the assay.[8,17,18]

Despite the simplicity of the Karmen method, the method requires serial readings in the ultraviolet. Since most instruments capable of making these measurements are very expensive, many institutions have encountered difficulty in including the serum transaminase assay as a routine clinical laboratory procedure. Steinberg and Ostrow[7] have shown that the assay may be carried out almost as accurately on the relatively inexpensive Bausch and Lomb Spectronic 20 Colorimeter calibrated by the manufacturer at 340 mμ. Henley and Pollard[19] have modified the Karmen method by utilizing the Tonhazy technique[20] of converting the oxaloacetate formed in the transamination reaction to pyruvate and then measuring the oxidation of DPN spectrophotometrically in the presence of reduced DPN and the more readily available lactic dehydrogenase. A simple colorimetric assay for the routine clinical laboratory determination of serum transaminase appears desirable, and methods of this type will shortly be reported.[21,22]

Normal Serum Transaminase Activity, Its Source and Disposition

Table 1 describes the serum transaminase activity of healthy adults as reported by several authors.

It will be noted in Table 1 that the normal serum transaminase reported by different observers agrees quite closely with the large series of LaDue and his associates, where a range of 5-40 units per milliliter was observed with a mean 22 ± 7 units per milliliter. All human sera tests to date have demonstrated the presence of transaminase. From the data available, it appears justifiable to set the upper limit of normal at 40 units per milliliter. Since duplicate assays are reproducible within 10 units per milliliter, it has been suggested that values of 41-50 units per milliliter be considered as borderline and values above 50 units per milliliter be considered as abnormally high.[9]

The normal serum level of transaminase activity appears to be fairly constant and independent of time of day or relation to meals or exercise.[7,9] The normal serum transaminase is also independent of sex or age (Table 1).

The source of transaminase in normal human sera has not been investigated, nor has it been isolated for a comparison of its physical or immunologic characteristics with purified tissue transaminases.

Little is known about the disposition of transaminase released into or present in serum. The presence of free transaminase in all human sera studied makes serum inhibition or inactivation unlikely. Evidence has been obtained that significant amounts of transaminase are not excreted into the urine even when the serum levels are abnormally high.[7,9] On the other hand, it has been previously suggested that biliary excretion may represent a normal route of transaminase excretion. This suggestion was based on the following: (1) Several specimens of normal human bile obtained at laparotomy had transaminase activities in the range of 2000 units per milliliter, or 100 times the serum level, and (2) serum transaminase assays were significantly elevated in patients with obstructive jaundice in the absence of laboratory evidence of the presence of hepatic necrosis.[9] Additional evidence supporting the concept of the biliary tree as a normal route for transaminase excretion has been derived from the following observations in experimental animals.

TABLE 1.—*Normal Serum Transaminase Activity**

Authors	No. Normals Studied	Range, Units/Ml.	Mean±S.D., Units/Ml.
Wróblewski et al.[4]	500	5-40	22±7
Kattus et al.[5]	11	16-24	20
Steinberg et al.[7]	20	10-33	
Chinsky et al.[9]	15	7-40	20±8
Nydick et al.[6]	75†	10-40	25±7

* Determined by the method of Karmen and expressed in terms of the unit defined by him. ‡ Includes males and females.
† Children.

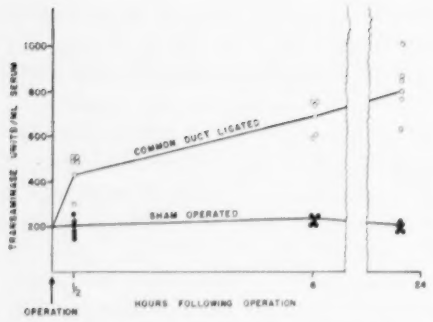

Fig. 1.—Effect of common-duct ligation on the serum transaminase of the rat. Solid circles represent values observed in sham-operated controls, and open circles refer to observations in common-duct-ligated animals.

1. Ligation of the common duct of rats is rapidly followed by a rise in the serum transaminase level, whereas sham-operated controls do not show significant changes in serum transaminase activity (Fig. 1). The changes in serum transaminase following common duct ligation were not associated with histological evidence of hepatic or cardiac necrosis.‖

2. Release of experimentally induced common duct obstruction in the rat is followed by a rapid return of the serum transaminase level to normal (Table 2).

‖ Dr. Herman Blumenthal performed the pathological studies, and Dr. Stanley Lang carried out the surgical procedures on these animals. Mr. Ray Wolff also collaborated in this study.

Results

Table 3 and Figures 2, 5, and 6 summarize the results obtained in the 701 cases studied. The cases shown in Table 3 have been divided into major disease categories. Under each category are shown the total number of cases studied, as well as the number of cases with normal, borderline, and high transaminase levels. Although multiple or serial determinations were obtained in most instances, the highest transaminase activity observed was used in constructing the Table.

Cardiac Diseases

Figure 2 summarizes our observations in 419 cardiac patients. The values noted represent the highest level observed during the course of the illness.

Acute Myocardial Infarction.—Two hundred twenty-two cases of acute myocardial infarction were studied. The electrocardiograms revealed the typical pattern of acute myocardial infarction in 169 instances. Thirteen others were proven to have acute infarction by autopsy, and the remaining forty patients had the diagnosis made on characteristic clinical findings.¶ It will be

¶ In each instance of this latter group of patients, the electrocardiogram was abnormal, revealing either subendocardial injury or bundle branch block, but was not considered to be diagnostic of an acute myocardial infarct. Nevertheless, the clinical diagnosis of acute myocardial infarction was made on the basis of typical chest pain, fever, leukocytosis, etc.

TABLE 2.—*Effect of Common Duct Ligation and Release of Obstruction on Serum Transaminase of the Rat*

Procedure	Serum Transaminase, Units/Ml.					
	Preoperative		6 Hr.	24 Hr.	24 Hr.	48 Hr.
Sham operated*	96	Ligation of duct	108	105	122	98
Duct ligated*	100		383	435	190	111
		Release of obstruction				

* 6 animals in each group. Values shown are the average for each group.

TABLE 3.—*Summary of the Serum Transaminase Activities of the Cases Studied*

Diagnosis	Total No. Cases	Transaminase Levels		
		Normal	Borderline	High
Acute myocardial infarction	222	4	5	213
A. ECG diagnostic	169	4	1	164
B. ECG not diagnostic	53	0	4	49
1. Autopsy evidence	13	0	1	12
2. Clinical evidence	40	0	3	37
Anginal syndrome	109	99	10	0
Cardiac arrhythmias	22	13	0	9
Acute pulmonary edema	27	19	7	1
Miscellaneous cardiac diseases	39	39	0	0
A. Chronic congestive failure	26	26	0	0
B. Pulmonary infarction	5	5	0	0
C. Benign idiopathic pericarditis	5	5	0	0
D. Myocarditis (toxic)	2	2	0	0
E. Subacute bacterial endocarditis	1	1	0	0
Hepatitis	21	0	0	21
A. Infectious mononucleosis	8	0	0	8
B. Infectious or serum hepatitis	13	0	0	13
Cirrhosis	19	6	1	12
Biliary obstruction	23	4	1	18
Pancreatitis	26	6	3	17
Metastatic carcinoma	30	15	2	13
Cerebral vascular accidents	15	13	0	2
Uremia	12	12	0	0
Postoperative	11	10	1	0
Traumatic injuries	13	8	2	3
Miscellaneous diseases	112	98	5	9

noted that in all but four of these 222 infarcts the transaminase level was above normal.

It has been observed [2,8,9] that the transaminase level becomes significantly elevated approximately 6 hours after the onset of chest pain, rising to a peak at about 24 hours. The levels then return toward normal, reaching the normal range on the third to the sixth day. The serial change in transaminase activity of a patient with acute myocardial infarction is shown in Figure 3.

The determination of transaminase has proven particularly useful in those patients suspected of having myocardial infarctions, in whom the electrocardiogram is equivocal or where the acute changes may be masked by the presence of bundle-branch block.[23] Case 1 (Fig. 4) illustrates the usefulness of serial serum transaminase levels in a patient with multiple myocardial infarcts who had an equivocal electrocardiogram.

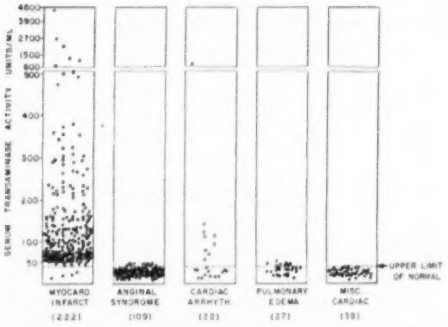

Fig. 2.—Serum transaminase levels in 419 cardiac patients. Each dot represents the highest level observed in a single patient. The number under each bar refers to the total number of patients in the particular category cited. The break in the bar denotes a change in the scale of the ordinate.

CASE 1.—A 62-year-old white man entered the hospital with severe chest pain. He gave a history of having had two previous myocardial infarcts—the last one 10 months previously. An electrocardiogram on admission was interpreted as revealing an acute high anterolateral infarction superimposed on old infarctions. The first specimen, obtained two days after admission, had an assay of 150 units per milliliter. The level gradually fell, reaching a normal range five days after the original pain. The patient did well for several days but on the eighth day had recurrence of chest pain and went into shock for several hours. A significant rise to an abnormally high transaminase level occurred. An electrocardiogram at this time revealed lateral extension of the infarction.

On the 26th hospital day another assay was done as a routine and was found to be elevated (162 units per milliliter). Several hours after this specimen had been obtained, the patient went into profound shock without any pain. Arterenol therapy was started and the patient maintained on this regimen for eight days.

Transaminase levels reached a peak of 1220 units per milliliter 12 hours after the initial elevation was noted. It then began to fall, finally reaching normal levels on the 33d day of hospitalization.

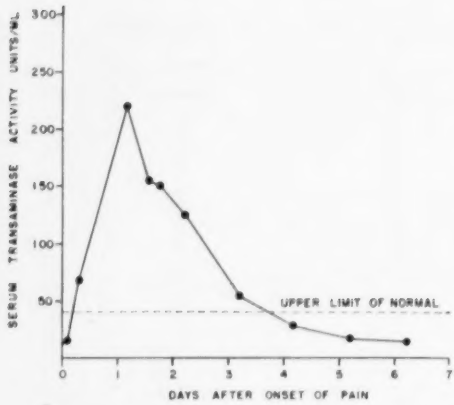

Fig. 3.—Serial serum transaminase levels in a patient with an acute myocardial infarction. Note that the level reaches a peak approximately 24 hours following the onset of pain and then returns to the normal range over the next few days.

On the 36th day, the patient again went into shock without pain and died. Although the electrocardiograms during the latter part of the patient's hospital course remained unchanged, autopsy revealed a large infarct, measuring 2.5 by 5 cm., over the left ventricle, which was dated as having probably occurred at the time of the striking changes in serum transaminase. In addition there were several other infarcts of various ages.

Of the 222 myocardial infarctions, 97% showed an abnormally high serum transaminase. When specimens were taken at proper time intervals, only one case of the entire group failed to develop a high value, or a correlation of over 99%. These results are in accord with the observations of LaDue et al.,[2,4] Steinberg and Ostrow,[7] and Kattus et al.[8]

The high correlation of elevated serum transaminase activity with myocardial infarction is further borne out by experimental studies in which graded myocardial infarctions were produced in dogs.[12,13] Agress et al.[12] showed that infarction of as little as 10%, or possibly less, of the total myocardium is associated with significant rises in transaminase levels. Most observers feel that there is a significant correlation between transaminase level and size of infarction.[4,12,13]

Although our data are still insufficient to correlate serum transaminase activity with size of infarct or prognosis, it was observed that those patients with levels above 200 units per milliliter were usually desperately ill and had a high mortality rate. Of 214 patients who survived the first day of their insult, 48 developed transaminase levels of greater than 200 units per milliliter. Twenty-five of these patients died (a 52% mortality), and an additional ten were in severe shock for protracted periods of time. In contrast, of 166 patients who did not reach levels of 200 units per milliliter, only 22 died (a 13% mortality), and the incidence of shock was much less.

Although our studies appear to show a relationship between height of activity and morbidity and mortality, LaDue et al. were unable to find any correlation in their studies on 50 patients with unequivocal acute myocardial infarction between height of activity and presence or absence of shock, or mortality rate.[4]

Anginal Syndrome.—Of 109 cases with the anginal syndrome, 99 had normal serum transaminase levels and 10 reached borderline levels. In no instance was a high level observed. In several of the cases, a significant serial change in serum transaminase (greater than 20 units per milliliter) occurred even though the maximal value did not exceed the borderline range.[9] In the light of experimental work[13,15] these changes might suggest the presence of small or subclinical findings.

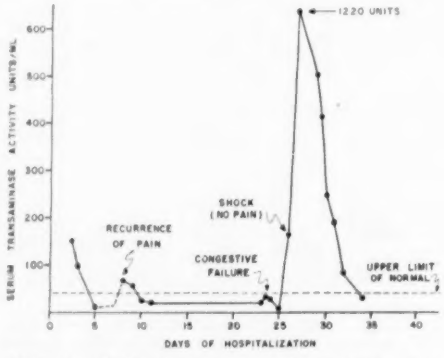

Fig. 4.—Serial serum transaminase levels in a patient (Case 1) with multiple myocardial infarcts and an equivocal electrocardiogram. See text for details.

The presence of a normal serum transaminase in angina pectoris has been reported by a number of investigators.[2,4,7,8,13]

Acute Pulmonary Edema.—Of 27 cases of acute pulmonary edema in which acute myocardial infarction was not the precipitating cause, the serum transaminase was normal in 19, borderline in 7, and elevated in 1. This latter case was complicated by the presence of a rapid auricular fibrillation. The finding of normal transaminase levels in the presence of acute cardiac failure has also been shown in studies carried out by LaDue et al.,[4] Steinberg and Ostrow,[7] and Kattus et al.[8]

Cardiac Arrhythmias.—Twenty-two cases with various cardiac arrhythmias were observed. This group included the following: Paroxysmal supraventricular tachycardia (7 cases), auricular fibrillation (4), flutter fibrillation (4), auricular flutter (3), ventricular tachycardia (2), and nodal tachycardia and Wolff-Parkinson-White (1 each). Nine of these cases had high transaminase levels. In all instances where high values were observed, the patients had a rapid arrhythmia (ventricular rate usually greater than 180 per minute). One of these patients died, and at autopsy although the heart was not remarkable there was marked centrilobular liver-cell necrosis. Another instance of this association, i. e., rapid arrhythmia, high serum transaminase (640 units per milliliter), and extensive centrilobular liver-cell necrosis at postmortem examination, was also observed in a patient at another institution.

Although the number of cases studied is still small, it appears that elevated transaminase values may be observed in association with very rapid arrhythmias regardless of type. The exact mechanism for the increase in serum transaminase is obscure, but we suspect that it is due to centrilobular liver-cell necrosis secondary to the diminished cardiac output of very rapid arrhythmias.

Miscellaneous Cardiac Diseases.—This group included 26 cases of chronic congestive failure, 5 cases of acute pulmonary infarction, 5 cases of benign idiopathic pericarditis, 1 case of subacute bacterial endocarditis, and 2 cases of acute nonspecific or toxic myocarditis. In no instance was a high level observed.

Observations similar to the above have been reported by other investigators.[2,4,7-9] Elevated levels, however, have been observed in acute carditis. Nydick and his group[6] studied 64 patients in various stages of rheumatic fever. In 15 patients, pathological studies were made either at autopsy or on biopsy specimens obtained during mitral commissurotomy. On the basis of their studies, Nydick et al.[6] reached the following conclusions: 1. Elevated serum transaminase levels occurred in some patients with clinical or histologic evidence of active rheumatic carditis. However, the levels were not consistently elevated in patients with active carditis and did not correlate closely with the clinical course or pathological findings. 2. Patients with severe cardiac involvement continued to have high levels even though they were given either acetylsalicylic acid or steroids. 3. Normal values were found in rheumatic patients who had no evidence of active cardiac involvement. 4. Normal values were seen in all patients after the acute rheumatic process subsided.

Although several authors have reported normal serum transaminase values in acute pulmonary infarction,[2,4] experimental ligation of the pulmonary artery in animals leads to increased serum transaminase activity.[15] Since pulmonary tissue does not have a particularly high concentration of the enzyme, the discrepancy between clinical and experimental observations may well be related to the amount of tissue involved in the infarcted area and suggests that extensive pulmonary infarction may elevate the serum transaminase value. In addition, the prolonged shocking episode occasionally seen in association with an extensive pulmonary infarct may also raise the transaminase through secondary centrilobular liver-cell necrosis. We have observed a patient who succumbed to a massive pulmonary infarc-

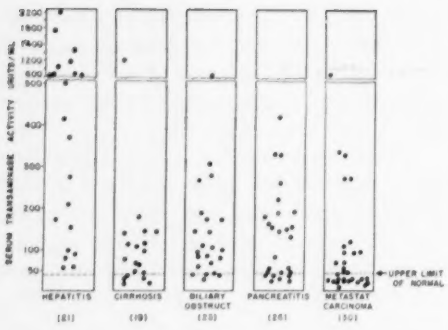

Fig. 5.—Serum transaminase levels in 119 patients with hepatic or biliary-tree disease. Each dot represents the highest level observed in a single patient. The number under each bar refers to the total number of patients in the particular category cited. The break in the bar denotes a change in the scale of the ordinate.

tion at another institution, where a significant elevation in serum transaminase (162 units per milliliter) occurred.

Hepatic and Biliary Disease

Figure 5 summarizes our observations in 119 patients with either hepatic or biliary-tree disease.

Hepatitis.—There were 21 cases of acute hepatitis. This included 10 patients with acute infectious hepatitis, 8 patients with hepatitis associated with infectious mononucleosis, and 3 patients with homologous serum hepatitis. All of these patients had elevated serum transaminase activities. In general, very high levels were observed in the first week of infectious and homologous serum hepatitis (508-2240 units per milliliter), and only moderately elevated values were observed in the patients with hepatitis associated with infectious mononucleosis (54-208 units per milliliter). In Figure 5 the lowest values shown in the hepatitis group represent patients with hepatitis associated with infectious mononucleosis.

In the uncomplicated case of infectious or serum hepatitis, the serum transaminase was initially observed to be very high during the first week of clinical illness, then rapidly fell over the next 7 to 10 days. The transaminase activity then continued to remain abnormally elevated (50-150 units per milliliter) for another one to four weeks before returning to the normal range. In the cases of infectious or serum hepatitis where the course has been protracted, persistently elevated values were observed. These observations are consistent with those reported by others.[2,5,7]

Friend et al. studied serum transaminase activity in experimental viral hepatitis in mice.[14] They observed a marked rise in the transaminase activity of all of their infected animals. There appeared to be a relationship between the rise in transaminase activity and the amount of virus inoculum, blood virus titer, and degree of liver necrosis. They concluded that although mouse hepatitis differs from human hepatitis in incubation period, histological changes, and natural course, both infections bring about comparable results in transaminase activity.

At the present time sufficient data are not available to correlate the serum transaminase level with other tests for hepatic function. Wróblewski and LaDue [5,25] noted that in several instances of infectious hepatitis the transaminase levels returned to normal before the usual liver function tests. In the light of experimental studies suggesting transaminase excretion by biliary mechanisms, it is possible that in hepatitis both hepatic-cell necrosis and deficient excretory mechanisms may contribute to the elevated serum transaminase. In the early stages of the disease, necrosis undoubtedly contributes most prominently to the elevation of the transaminase, but the subsequent persistence of a moderately elevated serum level may also be related to deficient excretory mechanisms.

Cirrhosis.—Twelve of nineteen cases of cirrhosis of the liver had high transaminase levels. The levels were elevated in those patients in whom there were other evidences of active inflammation and necrosis by biopsy or autopsy. Our observations are essentially in agreement with those previously reported by Wróblewski and LaDue.[5] In a study on 28 patients with cirrhosis (19

proven by biopsy), they observed 8 patients with normal serum transaminase levels and 20 patients with abnormally high levels. All the patients with elevated levels had laboratory evidence of hepatic dysfunction, and those with the highest levels had abnormal values on several different liver function tests.

The histological observations on three of our patients who had hepatic cirrhosis with normal serum transaminase levels are worthy of further comment. One of the patients died in hepatic coma, and autopsy revealed far advanced cirrhosis without evidence of acute necrosis. The other two patients were deeply icteric and had evidence of cirrhosis with marked fatty infiltration, but no areas of necrosis were observed (autopsy in one, liver biopsy in the other). These instances are cited to support the view that serum transaminase activity in hepatic disease correlates most closely with active cellular necrosis.

Obstructive Jaundice. — Twenty-three cases of obstructive jaundice were studied. The obstruction was associated with a common-duct stone in 12 instances, chlorpromazine (Thorazine) in 6, and carcinoma of the head of the pancreas in 5. Elevated transaminase levels were observed in 18 of the cases, a borderline level in 1, and normal levels in the remaining 4. In general, in those patients in whom the obstruction was protracted the transaminase level continued high but did not increase to the same extent as the bilirubin level. As a result only moderate elevations were observed even in patients with prolonged periods of obstructive jaundice. However, when the obstruction was relieved, the levels of serum transaminase closely followed the course of the serum bilirubin. The presence of an elevated transaminase in obstructive jaundice has been observed by others.[5,25,26]

Despite the lack of specificity of transaminase in differentiating obstructive jaundice from hepatic necrosis, it may be seen from Figure 5 that in contrast to the hepatitis group, the majority of patients with obstructive jaundice had values below 200 units per milliliter. In the one patient of the obstructive jaundice group who did have a very high value (600 units per milliliter), considerable suspicion existed as to the presence of an associated myocardial infarction. The data suggest that very high transaminase levels (i. e., above 400 units per milliliter) are more likely associated with hepatic necrosis than obstruction.

The observation of elevated serum transaminase levels in patients with biliary obstruction, despite the absence of hepatic necrosis, is consistent with our experimental observations on common-duct ligation in animals. Although the evidence suggests that the elevations noted in obstructive jaundice may be explained on the basis of interference of normal excretory mechanisms, the presence of normal transaminase values in some patients with obstructive jaundice and the lack of correlation between the rise in transaminase and bilirubin (previously referred to) indicate that other factors may be involved as well.

Acute Pancreatitis.—There were 26 cases in whom the diagnosis of acute pancreatitis was made. Only one of the cases was diagnosed as acute hemorrhagic pancreatitis (confirmed at autopsy). The remaining 25 patients were diagnosed as acute interstitial pancreatitis of the type commonly associated with biliary tract disease and having a high incidence of jaundice.

Of the group of 26 patients, 17 had an elevated serum transaminase activity. Almost all of the jaundiced patients had an elevated serum transaminase, whereas the majority of the nonjaundiced patients did not. A borderline range value was observed in the case of acute hemorrhagic pancreatitis. No correlation existed between the level of serum diastase and transaminase.

The data suggest that the rise of serum transaminase in patients with acute pancreatitis may not be due to pancreatic necrosis alone, but that biliary or hepatic factors may be involved as well.

Carcinomatosis.—Thirty cases of metastatic carcinoma were observed. Included among this group were Hodgkin's disease

and lymphosarcoma, as well as metastatic carcinomas arising from primary malignant diseases in the breast, lung, stomach, large bowel, pancreas, kidney, prostate, and uterus. Thirteen of the group revealed an elevated serum transaminase activity. In each instance of this latter group, hepatic metastases were demonstrated by either biopsy or postmortem examination. There were an additional three patients (two with borderline levels and one with a normal level) who were later shown to have hepatic metastases at autopsy. In the remaining 14 patients of the carcinomatosis group there was no evidence of hepatic involvement, and in each instance the serum transaminase was normal.

In our studies, the presence of an elevated serum transaminase in a patient with carcinoma was highly suggestive of hepatic metastases, although the absence of an elevated serum transaminase did not exclude hepatic metastases. Although our series is still small, the incidence of an abnormally elevated transaminase level in patients with hepatic metastatic carcinoma appears to be much greater than an abnormal elevation of the serum alkaline phosphatase. Wróblewski and LaDue[5] noted in their study of 22 patients with hepatic metastases that all but 2 of the patients had an abnormal transaminase level, that the transaminase was more consistently elevated than the alkaline phosphatase, and that the elevation in serum transaminase may be the only abnormal liver function test. They also noted that in 20 patients who had moderate to marked elevations of alkaline phosphatase secondary to bone metastases (in the absence of hepatic dysfunction) all had normal serum transaminase levels.

Other Diseases

Figure 6 summarizes the observations in the remainder of our cases, which are included in such categories as cerebral vascular accidents, uremia (both acute and chronic), operative procedures, traumatic injuries, and a miscellaneous group of diseases of infectious, inflammatory, metabolic, and degenerative origin.

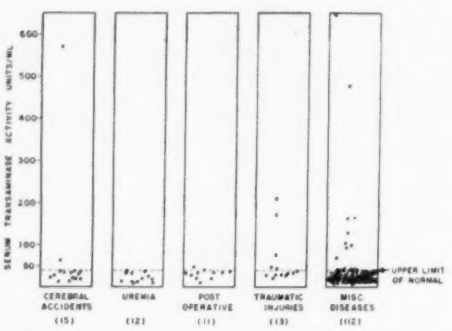

Fig. 6.—Serum transaminase levels in 163 patients with various diseases. Each dot represents the highest level observed in a single patient. The number under each bar refers to the total number of patients in the particular category cited.

Cerebral Vascular Accidents.—The serum transaminase was normal in 13 of 15 patients with an acute cerebral vascular accident. In two cases the serum transaminase was elevated (64 and 570 units per milliliter). These were the only two patients of this group to die, and at autopsy they were shown to have massive encephalomalacia. In a small series of patients with cerebral vascular accidents, Kattus et al.[8] found the serum transaminase to be normal.

Since brain tissue is rich in transaminase, yet a rise in serum transaminase is unusual following a cerebral vascular accident, some consideration was given to the possible liberation of the enzyme into the spinal fluid. For this reason we studied the spinal fluid transaminase in six patients 24 hours following the onset of a cerebral vascular accident and in an additional eight patients as follows: grand mal epilepsy (2), obstructive jaundice is semicoma (1), Bell's palsy (1), psychoneurosis (1), probably metastatic carcinoma to the brain (1), meningitis (1), thrombophlebitis with positive blood serology (1). Spinal fluid transaminase levels of 6, 13, 14, 16, 23, and 44 units per milliliter were observed in the six patients with acute cerebral vascular accidents.#

Serum assays on these patients were 12, 33, 36, 37, 33, and 64 units per milliliter, respectively.

The values observed in the control group were 12, 14, 14, 15, 20, 22, 36, and 36 units per milliliter. These observations suggest that significant liberation of transaminase into the spinal fluid does not occur in the 24-hour period following a cerebral vascular accident.

Uremia.—Twelve of our patients were uremic at the time of study. In eight of the cases, the uremia was secondary to chronic renal disease. Acute renal insufficiency was the precipitating cause in the other four. In all instances the serum transaminase activity was normal. Normal transaminase activity in uremia has also been reported by Steinberg and Ostrow.[7] These observations support the concept that deficient renal excretory mechanisms are not responsible for the appearance or maintenance of elevated serum transaminase levels.

Traumatic Injuries.—Thirteen patients with traumatic injuries were studied by analyzing single blood specimens obtained 24-36 hours after the injury. The transaminase levels were elevated in three, borderline in two, and normal in eight. The three cases with elevated levels included a stab wound of the abdomen with laceration of the liver (208 units per milliliter), a gunshot wound of the abdomen with laceration of the liver (171 units per milliliter), and an avulsion of the scalp with multiple fractures of the skull (75 units per milliliter). The two cases with borderline levels included a gunshot wound of the left thigh and a gunshot wound of the abdomen with perforation of the colon. The eight normal levels were observed in two cases of abdominal stab wounds and single instances each of multiple lacerations of abdomen and chest, stab wound of back, severed tendons of wrist, gunshot wound of chest, multiple fractures of jaw, and crush (steering wheel) injury to chest wall.

Although LaDue and his associates have demonstrated that skeletal muscle necrosis in man is associated with significant rises in serum transaminase,[25] our observations would suggest that in traumatic injuries significant elevations of the serum transaminase are uncommon unless the injury is extensive or the liver is involved. Of course any prolonged shocking episode may be expected to contribute to the elevation of serum transaminase through secondary centrilobular liver-cell necrosis.

Postoperative Levels.—Pre- and 24-hour postoperative serum transaminase levels were determined in 11 patients undergoing an abdominal laparotomy [cholecystectomy (6), hysterectomy (2), subtotal gastrectomy, colostomy, and lysis of small bowel adhesions (1 each)].

Preoperatively, all of the patients of this group had normal serum transaminase levels. Twenty-four hours following the abdominal surgery, the serum transaminase levels were only 1-8 units per milliliter higher than the preoperative level, and in all but one instance (preoperative 38 units per milliliter, postoperative 45 units per milliliter) the postoperative levels remained within the normal range.

Minor changes in the serum transaminase activity as a result of a surgical procedure in man has been previously commented on by Steinberg and Ostrow.[7] In animals, surgical trauma may be reflected in more significant changes in the serum transaminase activity.[13]

Miscellaneous Diseases.—There were 112 cases of miscellaneous diseases observed in our study. The diagnoses in these patients were as follows: acute cholecystitis (17), pneumonia (11), essential hypertension (5), acute gastroenteritis (5), psychoneuroses (4), lymphosarcoma (3), leukemia (3), cellulitis of foot (3), bronchial asthma (3), emphysema (3), ruptured aortic aneurysm (3), hydrops of the gallbladder (2), gangrene of extremity (2), disseminated lupus erythematoses (2), dermatitis (2), senile brain degeneration (2), pemphigus (2), and single instances of postoperative jaundice and shock, eclampsia, erythroblastosis fetalis, pernicious anemia (relapse), active duodenal ulcer, omental cyst, massive gastrointestinal hemorrhage, acute tonsillitis, acute cystitis, far-advanced active pulmonary tuberculosis, postoperative ischial

osteotomy, myeloid fibrosis, abdominal neurofibroma, heat exhaustion, severe osteoarthritis of spine, Mallory-Weiss syndrome, rheumatoid arthritis, ulcerated hiatus hernia, fibrous dysplasia, diabetic acidosis, myotonia congenita, salicylate intoxication, parathyroid disease, perinephric abscess, large-bowel obstruction, scleroderma, Charcot-Marie-Tooth syndrome, normal labor, hemorrhagic cyst of the adrenal, chronic granuloma of the liver, vascular thrombosis of spinal cord, aneurysm of pulmonary artery, diabetes mellitus, hyperthyroidism, C.N.S. syphilis, brain tumor, heat stroke, polycythemia vera, appendiceal abscess, and lung abscess in a patient with decompensated rheumatic heart disease (post valvulotomy). Among this diversified group, normal transaminase levels were observed in 98 of the cases, borderline levels were seen in 5, and high levels were found in 9.

In three of the patients with high levels, pathological studies demonstrating the common finding of liver-cell necrosis was present, and in five other instances where high levels were observed, it is quite probable that hepatic-cell necrosis existed.

Other investigators [2,7,8] have reported their observations on a wide variety of diseases. LaDue and his co-workers [4] noted elevated transaminase levels in some cases of acute myosits, and in skeletal muscle damage following arterial occlusion. Experimentally, infarction of the bowel in dogs has been shown to produce significant elevation in serum transaminase activity.[7] Since renal tissue is rich in transaminase, significant elevations in serum enzyme levels might be expected following renal infarction.

Comment on Shock.—Many of the patients included in this study had their transaminase levels assayed while they were in peripheral vascular collapse or following recovery from such an event. Almost all patients who were in shock for periods of greater than 24 hours developed elevated transaminase levels regardless of the underlying disease. In those patients who came to postmortem examination, well developed centrilobular liver-cell necrosis was present in each instance and presumably was the cause for the elevated transaminase. However, when the period of shock was of shorter duration, the transaminase level appeared to be independent of the vascular collapse and was primarily related to the underlying disease.

Comment

Since the initial report of LaDue and his associates [2] on the striking transient elevation of serum transaminase activity in acute myocardial infarction, considerable interest has been aroused in this assay as a diagnostic aid. The observations cited in this and other recent reports have attempted to clarify the significance of abnormalities in serum transaminase activity in relation to disease states. It is apparent that an elevated serum transaminase level is not specific for myocardial infarction and must be carefully interpreted in relation to a number of factors which may contribute to the serum transaminase activity. Despite the lack of absolute specificity for a particular disease state, the transaminase assay, when properly interpreted, has proven to be a very valuable adjunct to clinical diagnosis.

As a result of the observations on the glutamic oxaloacetic transaminase, several investigators have studied other enzymes which might prove more useful as a clinical diagnostic aid in determining the presence of active tissue necrosis. These include lactic dehydrogenase [27,28] and the glutamic pyruvic transaminase.[10,11,29] The latter appears to be more sensitive than the glutamic oxaloacetic transaminase in depicting acute hepatocellular damage and less sensitive as an indicator of acute myocardial necrosis. DeRitis et al.[10,11] have employed the ratio of the two transaminases (glutamic oxaloacetic and glumatic pyruvic) as a diagnostic aid.

Summary and Conclusions

The results of serum glutamic oxaloacetic transaminase assays in 701 patients

with a wide variety of diseases is reported and the literature relating to this assay reviewed.

Elevations in serum transaminase have been observed in patients with acute myocardial infarction, rapid cardiac arrhythmias, acute hepatitis, cirrhosis with active hepatic necrosis, biliary obstruction, acute interstitial pancreatitis, metastatic carcinoma to the liver, extensive traumatic injuries, and prolonged shock.

Although abnormal elevations in the serum transaminase activity occur in a number of disease situations, the level of serum transaminase, when carefully interpreted in relation to the factors and diseases known to influence the assay, has proven to be a valuable diagnostic aid.

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Respiration and the Regulation of Acid-Base Balance

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To understand the nature of disturbances in acid-base balance and the role of respiration in their initiation or compensation, it is necessary first to inquire into the operation of the blood buffer systems. The total "base" cations of the blood, B_t (chiefly $Na+$ and $K+$), are distributed among "acid" anions as follows:

$$B_t = BHCO_3 + BP + BA + BX$$

where P is protein, A is chiefly chloride, and X includes such things as phosphate, sulfate, and lactate. Now in a given blood subject to changes only in carbonic acid (or pCO_2), BA is constant and BX is negligibly small. We therefore concentrate our attention on that part of B_t which is distributed between HCO_3^- and P^-. Let us call this the "buffer base," B_b, and define it as follows:

$$B_b = BHCO_3 + BP = B_t - (BA + BX)$$

When carbonic acid is added to such blood, the total buffer base remains constant, but its distribution between HCO_3^- and P^- is altered according to the following equilibrium reaction:

$$BP + H_2CO_3 \rightleftarrows BHCO_3 + HP$$

or, since hemoglobin is the most important protein involved:

$$BHb + H_2CO_3 \rightleftarrows BHCO_3 + HHb$$

This equation tells us that when H_2CO_3 is 0 ($pCO_2 = 0$), all of B_b exists as BHb and none as $BHCO_3$. As increasing quantities of H_2CO_3 are added, B_b is transferred from Hb^- to form $BHCO_3$, and if pCO_2 got high enough, essentially all of B_b would exist as $BHCO_3$ and none as BHb. Thus hemoglobin is the most important blood buffer against H_2CO_3. The equilibrium states of this reaction can be represented graphically by plotting the so-called CO_2 absorption curve for true plasma from fully oxygenated blood. Such a curve for average normal blood is shown in Figure 1.

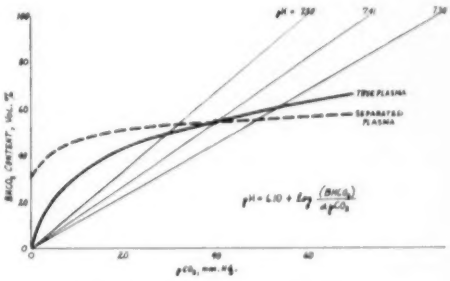

Fig. 1.—CO_2 Absorption Curves

We get this curve by exposing whole blood in glass tonometers at 37 C to gas mixtures containing known tensions of CO_2 and oxygen tensions sufficiently high to completely saturate the hemoglobin with O_2. After equilibrium has been attained, we centrifuge the blood anaerobically and determine the total CO_2 content of the plasma, from which we can calculate its $BHCO_3$ content. We then plot this $BHCO_3$ content against the pCO_2 of the gas mixture to which the blood was exposed. We call this true plasma because it was exposed to CO_2 while still in contact with its cells and thus reflects the buffer capacity of hemoglobin. If we had separated the plasma first and then exposed it to various pCO_2 levels, we would get a very different curve. This separated plasma curve is much flatter because the buffer capacity of hemoglobin is now lacking.

The pH corresponding to any given pair of values for pCO_2 and ($BHCO_3$) is defined by the familiar Henderson-Hasselbalch equation:

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$$pH_p = 6.1 + \log \frac{(BHCO_3)p}{\alpha pCO_2}$$

We note that the pH is dependent on the ratio of $BHCO_3$ to pCO_2. On our graph, iso-pH lines radiate from the origin, each line corresponding to a definite value of this ratio. It is important to note two things about this Henderson-Hasselbalch equation: First, it is directly applicable to plasma or serum and not to whole blood. If the CO_2 content were determined on whole blood, the equation could not be used unless correction factors were applied. Second, it is not the equation of the CO_2 absorption curve. It does not tell us what the $(BHCO_3)p$ would be at a given pCO_2. Every point on any curve that I drew on this graph would satisfy the Henderson-Hasselbalch equation, but the curves would not necessarily be CO_2 absorption curves for true plasma.

As we add carbonic acid to the blood by raising pCO_2, buffer base is transferred from hemoglobin to form bicarbonate. We move to the right along the curve, $(BHCO_3)$ rises, but relatively less than (H_2CO_3), so our pH falls. If we remove carbonic acid by lowering pCO_2, the reaction is reversed and we move back to the left.

We are now in a position to describe respiratory disturbances in acid-base balance (Fig. 2). Suppose that this curve represents the arterial true plasma of a patient. In vitro we altered pCO_2 by changing the composition of our gas mixtures in glass tonometers. In vivo the lungs act as our tonometer, and we change pCO_2 by changing the rate of pulmonary ventilation. In fact, the alveolar pCO_2 to which the blood is exposed is proportional to the ratio of metabolic CO_2 production to alveolar ventilation:

$$pCO_2 = \frac{K\,MR_{CO_2}}{V_A}$$

There is nothing mysterious about this: It simply says that the concentration of CO_2 in alveolar gas is equal to the quantity of CO_2 divided by the total volume of gas, just as the concentration of a sodium chloride solution is equal to the quantity of salt divided by the volume of solution. Normally, this ratio is such as to give us a pCO_2 of 40 mm. of Hg, and we have marked this as our normal point on the curve. The corresponding $(BHCO_3)$ is 54.5 vol.%, and the pH is 7.41. Now suppose that V_A increases for some reason (arterial anoxemia, hysteria, etc.) while MR_{CO_2} remains constant. We say that the patient is hyperventilating. His pCO_2 must fall, and hence we move to the left along our absorption curve. The $(BHCO_3)$ falls, the pH rises, and we have a respiratory alkalosis, or "primary carbonic acid deficit." Suppose, on the other hand, that V_A decreased for some reason (drug depression, obstruction, etc.). We say that the patient is hypoventilating. His pCO_2 must rise and we move to the right along the curve. The $(BHCO_3)$ rises, the pH falls, and we have a respiratory acidosis or "primary carbonic acid excess." We call these "respiratory disturbances" because they are brought about by changes in breathing. We also call them "carbonic acid disturbances" because it is the level of H_2CO_3 which the ventilation directly controls. Note something strange here: In respiratory alkalosis $(BHCO_3)$ is low, and in respiratory acidosis it is high. This behavior is exactly opposite to what we find in the more familiar metabolic disturbances which we must now examine.

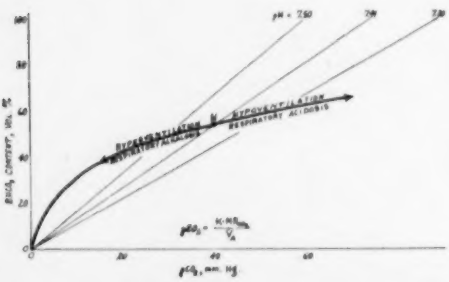

Fig. 2.—Respiratory Disturbances

Suppose that we take our blood at some fixed pCO_2 and add to it a certain quantity of a strong acid, HA (HCl, acetoacetic,

lactic, etc.). Recalling our definition of "buffer base"

$$B_b = BHCO_3 + BP = B_t - (BA + BX)$$

we note that when we add HA, B_b is reduced, because "base" is transferred from $BHCO_3$ to BA:

$$BHCO_3 + HA \rightleftarrows BA + H_2CO_3$$

If we now determine the CO_2 absorption curve we would find it displaced downward. If we had added $NaHCO_3$ (or removed HCl), we would find it displaced upward. We can now point out the essential difference between respiratory and metabolic disturbances. In the former, we have a primary change in H_2CO_3. This does not change the quantity of "buffer base" but only alters its distribution between HCO_3^- and P^-. We thus move along a given CO_2 absorption curve. In the latter, there is a primary change in the quantity of "buffer base" and we shift from one absorption curve to another. To know whether our absorption curve is in the normal position or not, we obviously must know the value of $(BHCO_3)$ at some fixed value of pCO_2. Let us select 40 mm. of Hg as this pCO_2 and define the corresponding $(BHCO_3)$ as the standard content. Then we can say that in respiratory acidosis or alkalosis $(BHCO_3)_s$ is normal (i. e., we move along the curve); but in metabolic acidosis $(BHCO_3)_s$ is low, and in metabolic alkalosis it is high (i. e., we jump from one curve to another).

How does respiration respond to metabolic disturbances in acid-base balance and what does its response accomplish? In Figure 4 we show what happens. Supposing

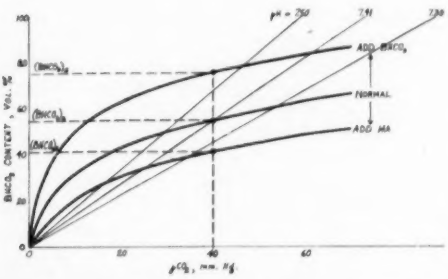

Fig. 3.—Metabolic Disturbances

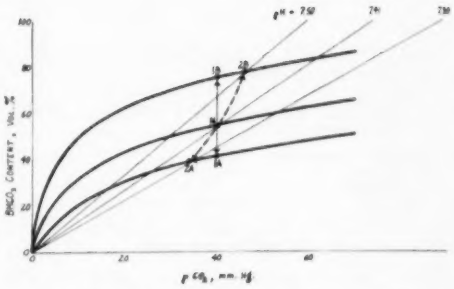

Fig. 4.—Respiratory Compensation for Metabolic Disturbances

we produced a metabolic acidosis sufficient to lower $(BHCO_3)_s$ to 41.0: If ventilation remained constant, then pCO_2 would be unchanged and we would find ourselves at point *1A*, where the pH is 7.28. But a fall in pH stimulates breathing and V_A rises. Hence the patient hyperventilates, pCO_2 falls, and we move to the left along our new absorption curve, thus raising the pH back toward normal. How far do we move? Obviously not as far as complete pH compensation, for if we did, our stimulus to breathing would disappear and we would begin to slide back again. Hence we settle down somewhere short of complete pH compensation, say at point *2A*, where pH is 7.32. Since the respiratory response is immediate, we do not actually move in these artificially separated steps, but rather along the continuous pathway shown by the dashed curve. Precisely analogous changes occur if we induce a metabolic alkalosis sufficient to raise $(BHCO_3)_s$ to 74.5. In this case, the rise in pH depresses ventilation and the patient hypoventilates and moves to the right along this new absorption curve thus lowering pH toward, but not quite to, normal.

Respiration thus provides an immediate, though incomplete, pH compensation in primary metabolic disturbances. What provides pH compensation in primary respiratory disturbances? The kidney, by excreting or retaining base, will slowly but completely compensate for a chronic respiratory disturbance. In effect, a metabolic

Features of Blood Chemistry Which Characterize Disturbances in Acid-Base Balance

	pCO_2	pH	$(BHCO_3)$	$(BHCO_3)s$
A. Respiratory disturbances				
1. Acidosis	+	−	+	N
2. Alkalosis	−	+	−	N
3. Compensated acidosis	+	N	+	+
4. Compensated alkalosis	−	N	−	−
B. Metabolic disturbances				
1. Acidosis	−	−	−	−
2. Alkalosis	+	+	+	+

acidosis is produced to compensate a respiratory alkalosis or a metabolic alkalosis to compensate a respiratory acidosis.

We can finally summarize some features of the blood chemistry which characterize the various disturbances in acid-base balance. Note particularly that a $(BHCO_3)$ determination alone (or an "alkaline reserve" which tends to parallel it) cannot distinguish between acidosis and alkalosis, for it is low in both metabolic acidosis and respiratory alkalosis and high in both metabolic alkalosis and respiratory acidosis. If both pH and $(BHCO_3)$ are determined and pCO_2 calculated, one not only can distinguish an acidosis from an alkalosis but can also determine whether the disturbance is respiratory or metabolic.

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Cold Agglutinins in Listeria Monocytogenes Infections

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Cold agglutinins were demonstrated in the serum of a patient with Listeria monocytogenes meningitis recently studied by us. The titers of cold agglutinins were significant and tended to parallel the titers of Listeria antibodies. False-positive heterophil antibody tests were easily produced by the cold agglutinins as described previously by Zarafonetis.[1] Further serological studies were done to evaluate the relationship between Listeria and cold agglutinins. This patient's course was also considered sufficiently unusual to report in some detail.

Infectious mononucleosis has been disputedly related to L. monocytogenes during the last 27 years. Shortly after these Gram-positive bacilli were identified and described as causing a marked monocytic reaction in animals, Nyfeldt, in Copenhagen, reasoned that here at last was the likely etiological agent of infectious mononucleosis. Investigation of all his patients with this disease soon proved rewarding, as he isolated a culture of L. monocytogenes from the blood of one such patient in 1929. He and several others confirmed this finding in the following years. The association of elevated titers of Listeria antibodies and positive Paul-Bunnell tests was investigated repeatedly with conflicting results. Girard and Murray [2] carefully and extensively reviewed this entire subject in 1951 and concluded that there are probably different diseases that appear clinically as infectious mononucleosis.

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Report of a Case

A 61-year-old man, a tailor, entered our hospital complaining of back pain of three months' duration. He was slightly confused on entry, and his answers were vague. He had been hospitalized elsewhere three years previously and again four months prior to entry, for "arthritis" of the back. He had been drinking beer excessively in the past few years and during the last year had a poor appetite and had lost 20 lb. in weight. He had had vague abdominal distress and backache for several months. Because of increasing fatigue and general weakness he had quit his work three months ago. He had had frequent headaches for several weeks or months also. For several days before admission he recalled having a "cold," with feverishness and night sweats.

Past history revealed ligation of varicose veins in 1918 and a hernia repair in 1932.

On examination he was found to be a poorly nourished, elderly, white man of small stature. He appeared weak and chronically ill, holding his head frequently and complaining of headaches. There was questionable slight terminal rigidity of his neck on entry. Dorsal kyphosis was noticeable, with slight decrease in motion of his thoracic spine. The edges of the tongue were smooth. The few remaining teeth were in poor condition. The throat was slightly inflamed. There was a minimal increase in the anteroposterior diameter of the chest, with a decrease in breath sounds. The heart was normal. The abdomen was flat and soft; the liver was tender and palpable 4-5 finger-breadths down from the costal margin. A few spider nevi were present on the upper part of the chest and on the arms. Temperature, 101 F; pulse, 96; respirations, 20, and B. P. 128/70.

The leukocyte count on entry was 10,500, with 70% neutrophils; the erythrocyte count was 3,300,000, with 11.0 gm. of hemoglobin. The cardiolipin flocculation test and urinalysis were negative. A chest x-ray on entry showed only a

TABLE 1.—*Total Leukocyte and Differential Counts*

Date	Total	Neutrophils, %	Lymphocytes, %	Monocytes, %	Basophils, %	Eosinophils, %
5-19	10,500	70	12	12	--	--
5-25	28,400	45	43	9	--	3
5-27	26,000	39	56	5	--	--
6-2	24,700	37	59	3	--	--
6-7	25,900	36	62	1	1	--
6-16*	21,600	42	53	5	--	--
6-21*	14,800	45	50	4	--	1
6-25	23,000	43	51	4	1	1
7-7	15,600	29	58	7	2	4
7-20	14,100	34	60	4	2	--
7-29	14,400	48	47	5	--	--
9-3	17,800	24	73	2	1	--
10-12	11,200	33	59	5	1	4
12-1	17,200	39	53	4	--	4

* Blood transfusions were given between June 16 and June 21.

moderate increase in the hilar and bronchovascular markings.

During the first two hospital days the patient became more acutely ill, with a temperature of 103 F and increasing lethargy and weakness. Physical evidence of meningitis became more prominent, and a lumbar puncture revealed a slightly turbid fluid with a pressure of 200 mm. This spinal fluid had 588 cells/ cubic millimeter, with 430 neutrophils and 158 lymphocytes; the protein level was 198 mg/100 cc.; the sugar, 75 mg/100 cc.; the Kolmer test was negative, and the colloidal gold curve was normal. Initially the smear and cultures showed small pleomorphic bacilli, apparently Gram-negative, and considered to be most likely a Hemophilus species. Streptomycin, 2 gm. daily, and crystalline penicillin, 1,000,000 units per two hours and later procaine penicillin, 600,000 units every six hours, caused a definite improvement, and within four days the patient was alert and afebrile. After therapy had been started and his symptoms were subsiding, further bacteriological studies revealed that the bacteria present in the spinal fluid were L. monocytogenes. These data and the serological studies are discussed below. A blood culture obtained at the time of the lumbar puncture revealed no growth. Leukocytosis and lymphocytosis in the blood were marked (Table 1).

After the initial improvement the patient remained afebrile, and his appetite, weight, and strength gradually increased. He continued to have intermittent headaches and mild diarrhea for several weeks. A barium enema and upper gastrointestinal tract roentgenographic examinations were normal. Roentgenograms of the chest, skull, and pelvis were not remarkable. Films of the thoracic and lumbar vertebra showed moderate osteoporosis with several compression type deformities. Serum calcium was 11.4 mg/100 cc. and phosphorus 3.9 mg. Sternal marrow examinations revealed a significant increase in lymphocytes and plasma cells. An electrocardiogram was normal. Repeat spinal fluid examinations revealed no abnormalities. The persistent lymphocytosis is shown in Table 1. The serum proteins and liver function studies are recorded in Table 2. A liver biopsy was attempted in view of the patient's hepatomegaly, hyperglobulinemia, and hyperphosphatemia, and the frequency of hepatic lesions found in experimental animals with miliary Listeria infections. Unfortunately the patient suddenly moved during the procedure and no specimen was obtained. Later that day he developed an intraperitoneal hemorrhage, which required blood transfusions. Following this episode the patient continued to improve gradually without further antibiotic therapy.

Two months later he returned to the hospital complaining of backache again and general weakness. He also had vague abdominal and chest pains. Physical examination was not helpful, and he had no fever in the hospital. It was surprising to find that cold agglutinins were again present in a very high titer (Fig. 1) and that Listeria agglutinins

TABLE 2.—*Serum Protein and Liver Function Studies*

Date	Albumin, Gm./100 Cc.	Globulin, Gm./100 Cc.	Alkaline Phosphatase, Bodansky Units	Thymol Turbidity, Units	Cephalin Flocculation	Sulfobromophthalein Retention, %
5-20	3.1	4.4	13.6	4.7	Negative	6.5
6-7	--	--	15.9	3.4	--	--
6-16	3.6	3.4	11.0	--	--	--
6-22	--	--	12.9	2.4	Positive	6.5
7-7	3.7	5.4	17.2	--	--	7.5
7-20	3.7	3.8	14.3	--	--	--
7-29	4.3	4.5	17.1	--	--	--

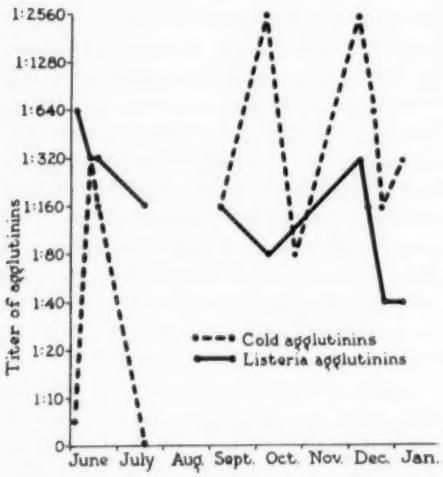

Fig. 1.—Serum agglutinin levels in patient during acute illness (June) and recurrent illnesses (October and December).

were still elevated. With only rest and analgesics he improved slowly and again left the hospital.

Approximately one month after his last admission and six months after his acute illness he returned to this hospital with vague chest and abdominal pains, general weakness, anorexia, slight dyspnea, and occasional vomiting. He denied the ingestion of any alcohol in the previous six months. At this time his cold agglutinins had again risen to very high levels, and the Listeria agglutinins were also increased. (Fig. 1). He spontaneously became asymptomatic within a few weeks and has remained in good health except for occasional mild backaches for the following year.

Bacteriological Studies

The organisms grew well, but slowly, on ordinary laboratory media. After 24 hours' incubation the colonies were very small and nonhemolytic; at 48 hours they were larger, approximately 1-2 mm. in size, and had developed a definite zone of β-hemolysis. Microscopically the organisms resembled diptheroids; they were pleomorphic Gram-positive bacilli (at times decolorizing fairly easily) occurring singly, in pairs, short chains, and "palisade formation." The appearance of the organisms varied greatly with the age of the culture.

The culture produced acid but no gas from dextrose, lactose, sucrose, maltose, salicin, trehalose, levulose, and rhamnose, but did not ferment mannitol, zylose, arabinose, or inositol. The organism did not liquify gelatin or produce hydrogen sulfide or indole. Motility was slight.

The virulence of the organism was demonstrated in rabbits. Intravenous innoculation produced death in 48-72 hours. The organism was recovered from liver, spleen, and heart blood of these animals.

Serological Studies

Materials and Methods

Three L. monocytogenes cultures were used in this study, one from our patient's spinal fluid, one obtained from the University of Illinois College of Medicine, and one from Mount Sinai Hospital, Chicago. These bacteria were retested for identification and virulence by injecting intravenously 1 ml. of an eight-hour broth culture into rabbits and swabbing the eyes of other rabbits with these eight-hour cultures. The former rabbits all died within 72 hours, and the latter all developed a purulent keratoconjunctivitis in the typical manner described by Anton and by Julianelle.[8]

Heat-killed 24-hour broth cultures of Listeria were used for the agglutination studies. Aliquots of these cultures were added to 0.5% phenolized saline and to 0.2% formalized saline. The former then represented the somatic and the latter the flagellar antigens of Listeria. All titrations were done in saline, using twofold dilutions, and the end-result expressed as the highest dilution showing macroscopic agglutination. One-tenth milliliter of a suspension of Listeria containing approximately 2,500,000,000 bacteria per milliliter

TABLE 3.—*Serum Agglutination Tests for Listeria Monocytogenes* *

	Date			
	6-3	6-14	6-17	7-19
Somatic antigen				
1	1:640	1:320	1:80	1:80
2	1:640	1:320	1:160	1:160
3	Neg.	Neg.	Neg.	Neg.
4	Neg.	Neg.	Neg.	Neg.
5	Neg.	Neg.	Neg.	Neg.
Flagellar antigen				
1	1:640	1:320	1:320	1:160
2	1:1,280	1:320	1:320	1:160
3	1:640	1:320	1:320	1:160
4	1:160	1:40	1:40	1:10
5	1:80	1:40	1:40	1:10

* 1 indicates Listeria isolated from patient; 2 and 3, cultures from 1 injected into rabbits and subsequently recovered; 4, Listeria from Mt. Sinai Hospital; 5, Listeria from University of Illinois College of Medicine.

TABLE 4.—*Erythrocytic Agglutination of Patient's Serum*

Serum Sample	Cold Agglutination		Davidsohn Heterophil
	Human Erythrocytes	Sheep Erythrocytes	
6-3	1:7	1:56	Negative
6-14	1:224	1:112	Negative
6-17	1:112	1:112	Negative
7-19	Negative	Negative	Negative

was added to all Listeria agglutination. These agglutination studies were incubated overnight at 5 C but were warmed at 37 C for a half hour before they were read.

The stimulation of antibodies in the rabbits was accomplished by intravenous injections of a saline suspension of approximately 5,500,000,000 heat-killed Listeria bacteria per milliliter. The rabbits were periodically bled by cardiac puncture, and serum was immediately separated from the clot. Cold agglutination of the rabbit sera was done by adding 0.1 ml. of a 2% suspension of the rabbit's own cells to its own serum.

Results

The titers of Listeria agglutinins present in the serum of our patient during his acute illness are shown in Table 3. Significant titers were demonstrated with the flagellar antigens of all the Listeria cultures obtained. One month after the acute illness the levels were still definitely elevated.

The titers of cold agglutinins to human erythrocytes present at the same time in this patient's serum are shown in Table 4 in the first column. In the next column are the levels of agglutination produced in the cold by this patient's serum and sheep erythrocytes (the Paul-Bunnell heterophil-antibody test). Incubating the above agglutination tubes at 37 C for a half-hour before reading eliminated the agglutination. Column 3 shows the titration of the serum with sheep cells at 25 C. This demonstrates the need for the exclusion of cold agglutinins as a factor in "false-positive" heterophil tests as emphasized by Zarafonetis.[1,15]

Repeated examinations of this patient's serum during the next seven months revealed persistent titers of Listeria agglutinins (Fig. 1). Cold agglutinins were also present in fluctuating titers. The rises in cold agglutinins were noted to occur during the periods when the patient also had mild recurrent illnesses of a nonspecific nature. The Listeria agglutinins were also more elevated during one of these recurrent episodes. The significance of these results is difficult to evaluate but suggested to us that perhaps this patient had a chronic form of listeriosis with exacerbations and remissions. He had no further antibiotic therapy after the initial acute illness.

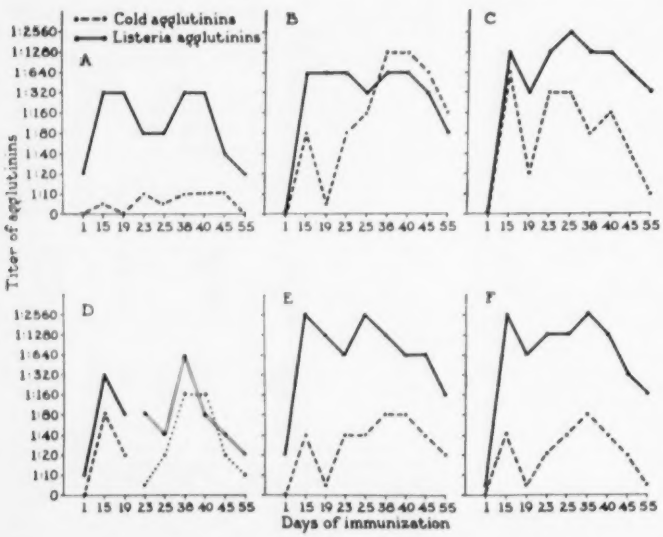

Fig. 2. — Agglutinins produced in rabbits by Listeria monocytogenes. Please note the parallelism of the cold agglutinins to the Listeria agglutinins. Rabbit D (the solid lines and dashes) died of hemorrhage following a cardiac puncture. A seventh rabbit (the open lines and dots in Space D), previously immunized, was substituted for completeness and given the booster and challenging doses as described in text.

The injection of nonviable L. monocytogenes into rabbits stimulated antibodies similar to those demonstrated in our patient. The results of this study are shown in Figure 2. Rabbits A and B were injected with Listeria cultured from our patient, C and D with Listeria obtained from Mount Sinai and E and F with Listeria from the University of Illinois. The rabbits were injected on the first, third, and eighth days with 1 ml., 2 ml., and 2.5 ml., respectively, of saline suspensions of heat-killed Listeria. On the 20th day "booster" doses of 1 ml. of these suspensions were given. It can be seen that both Listeria and cold agglutinins were produced by all three Listeria strains in all the rabbits.

On the 31st day challenging injections of 1 ml. of an 8-hour broth culture of viable L. monocytogenes were given to the six rabbits. These rabbits showed no changes other than a secondary rise in the agglutinins, as shown in Figure 2. Other rabbits with no previous immunization died within 72 hours after injections of the same amounts of the viable Listeria.

Absorption studies were done on the patient's serum with its high titers of cold and Listeria agglutinins, an immunized rabbit's serum with high titers of both agglutinins, and a commercial sample of serum containing cold agglutinins. The results of these studies are shown in Table 5. It can be seen that absorption of the cold agglutinins with erythrocytes at 5 C also reduced the titer of Listeria agglutinins. Similarly absorption of the Listeria agglutinins with Listeria at 37 C reduced the amount of cold agglutinins present in the serum. Neither the Listeria nor the erythrocytes absorbed out all the agglutinins. Guinea-pig-kidney absorption lowered the titers of the Listeria and the cold agglutinins in the serum.

TABLE 5.—*Absorption Studies*

	Listeria Agglutinins	Cold Agglutinins
Patient's serum		
Unabsorbed	1:160	1:640
After Listeria absorption	1:5	1:320
After erythrocyte cold absorption	1:40	1:10
Agglutinins from elution of cold erythrocytes	1:5	1:160
After guinea-pig-kidney absorption	1:80	1:10
Immunized rabbit serum		
Unabsorbed	1:640	1:1,280
After Listeria absorption	1:80	1:320
After erythrocyte cold absorption	1:160	Negative
Agglutinins from elution of cold erythrocytes	1:10	1:160
After guinea-pig-kidney absorption	1:160	1:80
Commercial serum with cold agglutinins		
Unabsorbed	Negative	1:320
After Listeria absorption	Negative	1:320
After erythrocyte cold absorption	Negative	1:80
Agglutinins from elution of cold erythrocytes	Negative	1:80
After guinea-pig-kidney absorption	Negative	1:80

Comment

Listeriosis had been previously considered to be primarily a disease of animals, having been reported in many species throughout the world. Recently, however, the more frequent occurrence of listeriosis in man has been emphasized.[4] Acute and usually fatal meningoencephalitis was the first and has been the commonest syndrome described. Occasional patients with septicemia, conjunctivitis, and subacute bacterial endocarditis have been reported.[5] Several writers[6-9] from Germany and elsewhere[10] in the past few years have stressed the role of Listeria in causing intrauterine infection resulting in fetal or neonatal death (granulomatosis infantiseptica). Postmortem examinations of the infants usually show miliary focal necrosis, especially in the liver, and Listeria organisms are easily isolated from the meconium, blood, cerebrospinal fluid, or brain. Similar observations have been described in sheep, cattle, horses, and rabbits.[11-12] Although little is known of the epidemiology of listeriosis, the recent studies of Gray and co-workers[13] demonstrated that abortion, stillbirth, and the early death of young rabbits could be produced by the ocular instillation of Listeria or by drinking water contaminated by Listeria. It is indeed interesting that many of the women with abortions or early infant death due to Listeria infections reported from Germany drank raw cow or goat milk.[6] Similarly, Hagemann[9] assumed that animals were the source of infection, as all

14 of his fetal deaths occurred with women living in agricultural areas. Another case of fatal meningitis apparently transmitted from sheep to man has also been reported.[14]

Despite the increasing numbers of cases reported and the increased interest in this disease and its epidemiology, the relationship of L. monocytogenes to infectious mononucleosis has remained unclear. Early reports stressed the frequency of positive Paul-Bunnell tests in association with increased titers of Listeria antibodies. Attempts to produce heterophil antibodies by the innoculation of killed L. monocytogenes into human volunteers, however, have failed. Similarly, the injection of living organisms into monkeys caused only a rapidly fatal meningoencephalitis.[2]

In most of the previous reports of positive heterophil antibody tests associated with Listeria infections, the Paul-Bunnell test was used. In the original description of this test, the tubes were read directly after overnight refrigeration. Zarafonetis showed earlier[1] and recently again[15] has emphasized that cold agglutinins can be a source of false-positive heterophil agglutinations. The use of the Davidsohn modification of incubation at 25 C for two hours prior to reading or the method of guinea-pig-kidney absorption are essential to eliminate this source of error.

Cold agglutinins to human and sheep cells were found in our patient with L. monocytogenes meningitis. The rise and decline of the titers of the cold agglutinins tended to parallel the fluctuations of the Listeria agglutinins. Injection of killed Listeria organisms into rabbits produced significant titers of cold agglutinins as well as Listeria agglutinins. In addition, these rabbits were protected from a lethal dose of living Listeria organisms. Absorption studies of the patient's serum with high titers of both agglutinins showed an immunological relationship of the two agglutinins. These observations suggest that both cold agglutinins and Listeria agglutinins can be produced in man and rabbits by the common strain of L. monocytogenes.

The high titer of cold agglutinins in our patient produced significant titers of "heterophil antibodies," using the original Paul-Bunnell procedure. In view of the foregoing, previous reports of the presence of "heterophil antibodies" in either proved Listeria infections or in presumed infectious mononucleosis must be guardedly interpreted. It is interesting to note that one of the first patients reported by Bunnell[16] to illustrate the value of the heterophil antibody test in infectious mononucleosis had "diphtheroid-like organisms" isolated from a blood culture.

The nonspecificity of cold agglutinins has been stressed in the past.[17] They have been found in low titers in patients with numerous diseases. High titers of cold agglutinins were first seen frequently in trypanosomiasis. Later, Peterson, Ham, and Finland[18] and others emphasized their occurrence in primary atypical pneumonia. The association of cold agglutinins with acquired hemolytic anemias was noted by Dameshek.[19] Also of interest are the extremely high titers that have been reported with peripheral vascular disorders.[20] Low titers (1:80 or less) of cold agglutinins have been observed in hospital patients with numerous acute and chronic conditions, including the common cold, bacterial infections, drug reactions, and leukemias.[17] The origin and significance of cold agglutinins are not well understood. It has been shown that the cold agglutinin is a globulin that moves with the γ-fraction by serum electrophoresis.[21] Rous and Robertson[22] produced cold agglutinins in rabbits by the injection of repeated small blood transfusions. Marienberg[23] innoculated rats, rabbits, and guinea pigs with trypanosomes and later demonstrated cold agglutinins in their sera. Removal of the spleen resulted in decreased levels of cold agglutinins and in increased numbers of the trypanosomes. Thus, the author believed that the reticuloendothelial system played a significant role in the formation of cold agglutinins in re-

sponse to infections. The most tenable concept at this time would seem to be that cold agglutinins represent a type of immunological response to various antigens.

Although our patient apparently had an acute infection (meningitis) caused by L. monocytogenes, several unusual features are worthy of note. The prominent and persistent lymphocytosis which he demonstrated has rarely been described in man. (The descriptive term, "monocytogenes," of Listeria is derived from its ability to produce a definite monocytosis in certain animals, especially the rabbit.) In addition, our patient had a significant titer of Listeria agglutinins for many months. During this time he had two nonspecific illnesses characterized by weakness, anorexia, and vague abdominal and chest pains. These possible relapses were associated with very high titers of cold agglutinins. Repeated blood, spinal fluid, and bone marrow cultures were negative, and no other definite evidence of any infection could be found.

Cases of chronic Listeria infections have been described infrequently. Schultz et al.,[24] in one of the first reports of a Listeria meningitis in man, described a patient with neurological and mental disturbances persisting for many months with gradual improvement and recovery. In this patient cultures of the spinal fluid revealed L. monocytogenes to be present for four months. Several Russian workers[25] have also described three patients with psychoses following L. monocytogenes infections. These patients had protracted fever, general weakness, irritability, insomnia, headaches, and other vague pains, as well as paranoid, hallucinatory, and depressive reactions that persisted for over two years. Portero and DeSpirito[26] reported a recurrent episode of Listeria meningitis several weeks after brief antibiotic therapy. These reports and the course of our patient suggest that the acute meningoencephalitis due to L. monocytogenes may occasionally be followed by a subacute or chronic state.

Summary

A patient with meningitis due to Listeria monocytogenes is reported. Significantly elevated titers of cold agglutinins as well as Listeria agglutinins were demonstrated in his serum. The cold agglutinins easily produced false positive heterophilantibody tests when the original method of Paul-Bunnell was used. The Davidsohn modification of incubating the tubes for two hours at room temperature before reading resulted in negative heterophil-antibody tests. The injection of heat-killed Listeria organisms into rabbits produced elevated titers of cold agglutinins. Absorption of this patent's serum, which contained high titers of both agglutinins, by either cold erythrocytes or Listeria organisms resulted in marked decrease of the other antibody. These serological studies suggest that L. monocytogenes can produce in man and rabbits high titers of cold agglutinins which are immunologically related to the Listeria agglutinins elicited. The cold agglutinins may then cause false-positive heterophil-antibody tests if the original Paul-Bunnell method is used. This observation may explain the difficulty in differentiating infectious mononucleosis from listeriosis in the past. The possibility of chronic listeriosis is discussed.

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Treatment of Staphylococcic Endocarditis

Report of Seven Cases

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Staphylococcic endocarditis is a difficult and frustrating therapeutic problem. The increasing number of penicillin-resistant strains,[1-4] the development of resistance during the course of therapy, and the fulminating and destructive nature of many staphylococcic infections combine to present the physician with an enormously difficult problem in clinical therapeutics.

While at one time the Staphylococcus was responsible for only 9.5% of all cases of bacterial endocarditis,[5] Dowling[2] feels that the staphylococcic is now second in frequency only to the streptococcic type.

Results of treatment have not been encouraging. In 1948, Guest and Harrison[7] were able to find but 12 instances of successful treatment of endocarditis due to Staphylococcus. Levinson, in 1950, reported 18 patients, with a mortality rate of 66%.[1] Dowling,[2] in 1952, reported 25 cases treated by penicillin, with a recovery rate of 52%. Fisher et al.[8] reported bacteriologic cure of 7 of 13 cases, or 54% survival.

The type and amount of antibiotics used by reporting physicians has varied widely. Cures have been reported on amounts of penicillin ranging from 10,000 units every two hours[9] to the 24,000,000 units daily suggested by Dowling.[2] In addition, other antibiotics used alone and in combination have been reported to effect cures.[10,11]

It is the purpose of this paper to report seven patients with staphylococcal endocarditis seen at Emory University Hospital on the cardiology service since 1951, in whom there were six cures, and further to outline a plan of therapy which we have found useful.

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Report of Cases

CASE 1.—A woman, aged 31, with a known heart murmur for five years, was admitted with a history of fever of four days' duration. Six blood cultures grew hemolytic Staphylococcus aureus, coagulase-positive. Sensitivity studies were reported as in Table 1.

TABLE 1.—*Results of Sensitivity Studies in Case 1*

	Grew in	Inhibited in
Penicillin	10 units/cc.	
Streptomycin	12.5 γ/cc.	25 γ/cc.
Chlortetracycline	Control only	
Oxytetracycline	Control only	
Chloramphenicol	3.1 γ/cc.	6.2 γ/cc.
Polymyxin	50 γ/cc.	
Bacitracin	Control only	

Studies from another laboratory were reported as showing growth in penicillin, 0.1 unit/cc. and inhibition in 0.5 unit/cc. Repeated studies in this laboratory did not confirm this report.

The significant physical findings were a Grade 2 systolic murmur at the apex, a palpable tender spleen, and petechiae in the conjunctivae and over the anterior chest.

Therapy was begun with chlortetracycline (Aureomycin), 250 mg. every six hours by mouth, while awaiting the results of sensitivity studies. The fever persisted, and on the fifth day chlortetracycline was discontinued and penicillin was begun in a dose of 90,000,000 units daily. Sixty million units was given by constant intravenous drip through an indwelling plastic catheter, with booster doses of ten million units diluted in 100 cc. of isotonic saline given into the tube every eight hours over a period of 31 days. Fifteen thousand units of bacitracin was given intramuscularly every six hours for 11 days. Streptomycin, in a dose of 1 gm. intramuscularly, was given every 12 hours during the last three weeks of therapy.

Fever due to drug sensitivity and to phlebitis occurred during the course of therapy, but re-

covery was complete and otherwise uneventful. She has remained well in a follow-up period of approximately four years.

Case 2.—A youth, aged 17, had congenital heart disease which was determined by catheterization studies to be pulmonic stenosis and interventricular septal defect. He developed evidence of bacterial endocarditis in December, 1951, and was treated in another hospital with 8,000,000 units of penicillin daily for eight weeks without benefit. He was admitted to Emory University Hospital May 29, 1952, where blood cultures were repeatedly positive for hemolytic Staphylococcus aureus, coagulase-negative. The sensitivity studies are shown in Table 2.

Table 2.—*Results of Sensitivity Studies in Case 2*

	Grew in	Inhibited in
Penicillin	20u/cc.	
Oxytetracycline	Control only	
Chlortetracycline	Control only	
Streptomycin	25 γ/cc.	50 γ/cc.
Chloramphenicol	0.75 γ/cc.	1.5 γ/cc.
Polymyxin	3.12 γ/cc.	6.25 γ/cc.
Bacitracin	0.1 unit/cc.	0.2 units/cc.

The significant physical findings were an enlarged heart with systolic propulsion of the precordium, a harsh Grade 4 systolic murmur and thrill maximal at the second and third left intercostal space, and splenomegaly extending 4 cm. beneath the costal margin.

Therapy with 60,000,000 units of penicillin daily by the intravenous route and 2 gm. of streptomycin was ineffective, and blood cultures were still positive after one week. Bacitracin, 1500 units intramuscularly every six hours for 12 days, and oxytetracycline (Terramycin), 500 mg. orally every six hours, caused a disappearance of fever, and the blood cultures became sterile.

He was discharged on therapy with oxytetracycline, which was continued for one week. Within 24 hours of discontinuing the drug, chills, fever, and positive blood cultures recurred.

He was readmitted and treated with 120,000,000 units of penicillin daily, plus probenecid (Benemid), 0.5 gm. four times a day, and 2 gm. of streptomycin daily for 28 days.

During the last 17 days he also received erythromycin, 600 mg. orally every six hours. He again relapsed, with positive blood cultures after three weeks, and on therapy with oxytetracycline, 2 gm. by intravenous drip, became fever-free in three days.

He was discharged on therapy of 250 mg. of oxytetracycline and 1 gm. of sulfisoxazole (Gantrisin) four times a day. He was continued on this therapy at home for five months. After omission of these drugs he remained asymptomatic, and blood cultures taken at intervals of two and three months remained sterile. He has been able to work regularly and has remained well over a follow-up period of four years.

Comment.—The duration of the staphylococcal endocarditis was approximately one year, and a cure could not be obtained in spite of massive chemotherapy with penicillin and multiple antibiotics. He was finally discharged on suppressive therapy with the hope that more effective antibiotics might be developed. It was surprising to find that a cure followed six months of such therapy. This suggests that host resistance may at times be a decisive factor in obtaining a cure when long-term suppressive therapy is utilized.

Case 3.—A man, aged 63, had been known to have a valvular heart disease since 1920. Three months prior to his admission on July 17, 1953, he began to have chills and fever, which subsided as long as he was given chlortetracycline. After admission, eight blood cultures grew hemolytic Staphylococcus aureus, coagulase-positive, and the sensitivities were reported as in Table 3.

Table 3.—*Results of Sensitivity Studies in Case 3 Before Therapy*

	Grew in	Inhibited in
Penicillin	0.1 units/cc.	0.5 units/cc.
Streptomycin	6.2 γ/cc.	12.5 γ/cc.
Chlortetracycline	Control only	
Oxytetracycline	Control only	
Chloramphenicol	3.1 γ/cc.	6.2 γ/cc.
Carbomycin	Control only	

Physical examination showed a Grade 3 systolic murmur at the apex and a few scattered petechiae over the feet.

Therapy was begun with 82,000,000 units of penicillin by intravenous drip and 1 gm. of streptomycin intramuscularly daily. Penicillin was discontinued for a brief period because of urticaria. Therapy with chlortetracycline, oxytetracycline, and carbomycin (Magnamycin) was ineffective. Penicillin was resumed in a dosage of 160,000,000 units daily, and in spite of a blood level of more than 2000 units per cubic centimeter, positive blood cultures could be still obtained. Sensitivity studies on this organism were as shown in Table 4.

Table 4.—*Results of Sensitivity Studies in Case 3 After Therapy*

	Grew in	Inhibited in
Penicillin	0.1 units/cc.	0.5 units/cc.
Streptomycin	6.2 γ/cc.	12.5 γ/cc.
Chlortetracycline	0.7 γ/cc.	1.5 γ/cc.
Chloramphenicol	0.7 γ/cc.	1.5 γ/cc.
Oxytetracycline	1.5 γ/cc.	3.1 γ/cc.
Carbomycin	Control only	

Erythromycin, 500 mg. every six hours for 13 days, was without effect. Bacitracin, 20,000 units intramuscularly every six hours, was begun three days before death. In spite of all therapy, his condition deteriorated, and he died after 58 days in the hospital and approximately 5 months after onset of the illness.

Autopsy showed bacterial endocarditis of the mitral valve, from which hemolytic Staphylococcus aureus, coagulase-positive, was cultured. There was not the expected massive destruction of the heart valves, which appeared normal except for two small vegetations.

Comment.—In spite of two reports of in vitro sensitivity to penicillin, the organism in vivo was quite resistant, and it was remarkable that positive cultures could be obtained when the blood level of penicillin was more than 2000 units per cubic centimeter. This demonstrates the wide discrepancy between test-tube observations and what may actually occur in the living subject.

CASE 4.—A youth, aged 19, had a Blalock operation for tetralogy of Fallot three years before admission on Sept. 29, 1953. He had had evidence of endocarditis for about five months. Blood cultures were positive for hemolytic Staphylococcus aureus, coagulase-negative. Sensitivity studies were reported as shown in Table 5.

TABLE 5.—*Results of Sensitivity Studies in Case 4*

	Grew in	Inhibited in
Penicillin	0.02 units/cc.	0.03 units/cc.
Streptomycin	Control only	
Chlortetracycline	Control only	
Oxytetracycline	Control only	
Chloramphenicol	0.7 γ/cc.	

The significant physical findings were moderate cardiac enlargement and a machinery murmur over the left upper chest, marked splenomegaly, and the physical characteristics of Marfan's syndrome.

He was given 50,000,000 units of penicillin by continuous intravenous drip plus 2 gm. of streptomycin and 2 gm. of probenecid daily. Treatment was continued for four weeks with complete recovery. He has remained well in a follow-up of two and one-half years.

Comment.—Endocarditis had been present for five months. The organism was quite sensitive, and the response to treatment was prompt and complete. In view of our previous experience with apparently sensitive bacteria, we were unwilling to hazard treatment with smaller doses.

CASE 5.*—A boy, aged 2 years, had congenital heart disease, thought to be an interventricular septal defect. He was admitted to Emory University Hospital on Nov. 2, 1953, after developing fever, malaise, nausea, and vomiting five days previously. Five blood cultures grew hemolytic Staphylococcus aureus, coagulase-positive. The sensitivity studies were reported as shown in Table 6.

TABLE 6.—*Results of Sensitivity Studies in Case 5*

	Grew in	Inhibited in
Penicillin	1 unit/cc.	5 units/cc.
Streptomycin	6.2 γ/cc.	12.5 γ/cc.
Chlortetracycline	Control only	
Oxytetracycline	Control only	
Chloramphenicol	1.5 γ/cc.	3.1 γ/cc.
Carbomycin	Control only	
Polymyxin	50 γ/cc.	
Bacitracin	Control only	
Erythromycin	Control only	
Neomycin	Control only	

Physical examination revealed one fresh petechia in the buccal mucosa and a normal-sized heart with a Grade 3 systolic murmur which was loudest in the third and fourth left intercostal spaces, parasternally. The spleen was enlarged and tender.

Therapy was initiated with 60,000,000 units of penicillin and 0.25 gm. of streptomycin daily. After five days, penicillin was discontinued, and the blood cultures were again positive. Erythromycin, 300 mg. daily, and streptomycin were ineffective. Oxytetracycline then was substituted for streptomycin, and on this regimen the fever decreased. This combination was continued for nine days, when diarrhea forced the discontinuance of oral medication. Erythromycin was administered by means of a constant intravenous infusion through a plastic catheter in a dose of 2 gm. daily with booster doses of 250 mg. intramuscularly twice daily. The temperature decreased to levels of 99-102 F. Phlebitis at the cut-down site was severe and proved to be the cause of persisting fever. After 12 days, erythromycin and oxytetracycline were resumed orally and the infusions discontinued. The low-grade fever subsided entirely, and therapy was continued for three more weeks in the hospital and for one month at home. The patient has remained asymptomatic in a follow-up of two and one-half years.

Comment.—Therapy with massive doses of penicillin did not control the infection; however, the combination of erythromycin and oxytetracycline intravenously and later orally in addition to streptomycin produced a bacteriologic cure. The confusion of fever

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due to phlebitis with persistent infection is well illustrated.

CASE 6.—A woman, aged 22, with known congenital heart defect, probably Eisenmenger's complex, was admitted to another hospital Aug. 30, 1954, with a history of fever and chills. Three blood cultures were positive for Staphylococcus aureus, coagulase-negative. Sensitivity studies on this organism were done at another laboratory and were reported as shown in Table 7.

TABLE 7.—*Results of Sensitivity Studies in Case 6*

Good Inhibition	Fair Inhibition	Minial Inhibition
60 γ oxytetracycline 60 γ chlortetracycline	60 γ chloramphenicol 20 units bacitracin	10 units penicillin 30 γ polymyxin

Treatment with 1,800,000 units of penicillin daily plus 400 mg. of erythromycin and 1 gm. of streptomycin daily was ineffectual, and patient was transferred to this hospital. Blood cultures taken on admission showed no growth.

Pertinent physical findings included clubbing of the fingers and cyanosis of the nail beds. There was a systolic propulsion of the lower sternum, a loud snapping pulmonary second sound, and a Grade 3 systolic murmur at the apex.

Therapy consisted of 80,000,000 units of penicillin daily, given in a continuous intravenous drip through a plastic catheter, 2 gm. of erythromycin added to the infusions, 1 gm. of streptomycin twice daily intramuscularly, and 0.5 gm. of probenecid four times daily. After two weeks the injectable erythromycin was discontinued because of irritation of the veins, and the drug was begun orally in a dosage of 0.5 gm. four times daily.

Therapy was continued for 28 days. Recovery was complete and uneventful in a follow-up of two and one-half years.

Comment.—Subsequent catheterization studies showed findings compatible with Eisenmenger's complex.

CASE 7.—A man, aged 58, with known rheumatic heart disease developed symptoms of endocarditis two months prior to his admission to another hospital on Sept. 10, 1954. Three blood cultures grew Staphylococcus albus, coagulase-negative. The sensitivity studies were reported as shown in Table 8.

He was treated at home with 12,000,000 units of procaine penicillin intramuscularly and 2 gm. of streptomycin intramuscularly daily for six weeks.

TABLE 8.—*Results of Sensitivity Studies in Case 7*

	Grew in	Inhibited in
Penicillin	3.1 units/cc.	6.2 units/cc.
Erythromycin	1.5 γ/cc.	3.0 γ/cc.
Chlortetracycline	6.2 γ/cc.	12.5 γ/cc.

On the day of admission to this hospital the patient had an acute syncopal episode with generalized convulsions and cyanosis. On regaining consciousness he was incoherent and irrational, and speech was slurred. All manifestations cleared within two or three hours.

Physical findings on admission included a negative neurologic survey, moderate cardiac enlargement, diastolic gallop rhythm, and the murmurs of aortic insufficiency, mitral stenosis, and mitral insufficiency.

In the hospital, antibiotics were withheld, and the temperature remained normal. Four blood cultures were sterile, and the patient was discharged asymptomatic. He has remained well on reexamination one year later.

Comment.—Although the therapy was successful, it is hazardous to use long-acting penicillin in the treatment of staphylococcal infections, and the total dose would ordinarily be considered dangerously small.

The embolus occurring after six weeks of successful therapy demonstrates that such an episode does not necessarily indicate that a cure is not being obtained.

Suggested Plan for Management

The signs and symptoms of bacterial endocarditis have been adequately presented

TABLE 9.—*Results of Therapy of Staphylococcal Endocarditis*

Case	Age, Yr.	Lesion	Therapy	Duration	Result
1	31	R.H.D.	90,000,000 units penicillin, 2 gm. streptomycin	37 days	Cured
2	17	I.V. septal; pul. sten.	120,000,000 units penicillin, 2 gm. streptomycin; discharged on 2 gm. oxytetracycline, 2 gm. sulfisoxazole for 4 mo.	8 mo.	Cured
3	63	R.H.D.	82,000,000-160,000,000 units penicillin, 1 gm. streptomycin; chlortetracycline, carbomycin, bacitracin, 3 days	2 mo.	Died
4	19	Tetralogy; Blalock opr.	50,000,000 units penicillin, 1 gm. streptomycin	4 wk.	Cured
5	2	I.V. septal defect	30,000,000-60,000,000 units penicillin, 1 gm. streptomycin, erythromycin, oxytetracycline	10 wk.	Cured
6	22	Eisenmenger complex	80,000,000 units penicillin, 2 gm. streptomycin, 2 gm. erythromycin	5 wk.	Cured
7	58	R.H.D.	12,000,000 units procaine penicillin, 2 gm. streptomycin	6 wk.	Cured

elsewhere.[12] It is worth reemphasizing, however, that early diagnosis is essential and that endocarditis must be suspected in every instance of unexplained fever or anemia, even though no heart murmur is present. Undue delay in initiating therapy may lead to valvular destruction, valve ring abscesses, focal myocarditis, mycotic aneurysms, and glomerulonephritis and negate all subsequent therapeutic measures. Blood cultures must always be obtained prior to institution of chemotherapy. Several cultures daily over a period of three days suffice in the usual case. Determination of sensitivity serves a useful purpose, but limitations of such tests should be kept in mind. Occasionally, therapy must be instituted in spite of negative blood cultures.

Fortunately, staphylococci grow readily, and positive cultures may be obtained earlier and with greater frequency than with other resistant bacteria, such as enterococci.

One must view every Staphylococcus as being highly resistant, even though in vitro tests may show an apparently sensitive organism. In other cases, in vitro tests may indicate resistance, but in vivo the response to therapy may be good. In view of this fact, it would seem desirable to use multiple antibiotics of the bactericidal type. Therapy should not be initiated with the tetracycline group of drugs alone, even though sensitivity studies may suggest their use. It is inadvisable to use repository penicillin preparations in the treatment of staphylococcal infections.

The treatment of choice in the management of staphylococcal endocarditis is penicillin, even where there has been a history of prior sensitivity reactions. Frequently the readministration of the drug is not associated with sensitivity reactions, or if present they may be mild and can be controlled by antihistamines. It would appear unwise to use corticotropin (ACTH) or cortisone over any period of time in the treatment of endocarditis. It is unwise to make unnecessary changes in therapy, and one should allow ample time for any given treatment schedule to be tested. In evaluating evidence of persistent infection, such as fever, one should keep in mind the importance of emboli, drug sensitivity, and phlebitis at the cut-down site as a cause of recurrent or persistent fever.

In patients in whom the presumptive or proved diagnosis of staphylococcal endocarditis is made, the initial therapy should consist of penicillin in massive doses given in a continuous intravenous drip through a cut-down, with booster doses at regular intervals given through the infusion tubing. Heparin may be added to the infusion to reduce thrombophlebitis at the cutdown site. The initial amount of penicillin should be at least 50,000,000 units by constant intravenous drip, with booster doses of 1,000,000 units every six hours. In addition, erythromycin, 500 mg. orally four times daily; streptomycin, 1-2 gm. intramuscularly daily, and probenecid, 0.5 gm. orally four times daily, should be given.

If there is no response on this regimen within three days' time, the dose of penicillin should be doubled and treatment continued for four more days.

If penicillin, erythromycin, streptomycin, and probenecid do not produce a clinical response in seven days' time, combinations of antibiotics, using bacitracin, chloramphenicol, neomycin, oxytetracycline, or chlortetracycline, should be used in addition to penicillin. The successful regimen should be continued for five to six weeks. In occasional cases where infection is suppressed but not eradicated, long-term treatment with oral broad-spectrum antibiotics is indicated.

Summary

Cures were obtained in six out of seven cases of endocarditis due to staphylococcal infection (Table 9). Therapy is discussed, and a suggested plan of treatment is outlined. The importance of massive doses of penicillin alone or in combination with other drugs is stressed.

Addendum

Two additional patients have been cured, using 40,000,000 units of penicillin

plus 2 gm. of streptomycin for four weeks in one instance and 22,000,000 units plus 2 gm. of streptomycin daily for three weeks in another instance.

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Leukocyte Agglutinins in Human Sera

Correlation Between Blood Transfusions and Their Development

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Introduction

The discovery of autoantibodies for erythrocytes in acquired hemolytic anemia (AHA)* and for platelets in idiopathic thrombocytopenic purpura (ITP) led to a search for antibodies for leukocytes in leukopenic persons. The observation by Moeschlin and Wagner in 1952 [1,2] of the presence of a leukoagglutinin in the serum of a patient with granulocytopenia following aminopyrine (Pyramidon) administration introduced a series of publications demonstrating agglutinins for leukocytes in human sera and the antigens of leukocytes. [3-23] The contributions of these studies were (1) the development of relatively simple techniques for the detection of leukoagglutinins, (2) a limited survey of disorders in which leukoagglutinins may be found, (3) a brief description of the properties of the antibody, (4) the production of leukopenia by passive transfer of the agglutinin, and (5) some characterization of the leukocyte antigens. The considerable body of findings presented in the publications left a number of key questions unanswered and raised many new problems as well. As yet, a clear-cut autoactivity of the majority of the leukoagglutinins has not been observed, the relation of the agglutinin to leukopenia is not consistent, the findings of the agglutinin in apparently unrelated disorders has not been explained, and the exact role of transfusions in the development of leukoagglutinins has not been provided.

Our observations, while reinforcing the growing restraint on interpretation, partially confirm the findings of other investigators and further extend the knowledge of leukoagglutinins in human sera. Data are presented on the incidence of leukoagglutinins in a selected number of primarily hematologic disorders, on the relations of leukopenia and transfusions to the presence of agglutinins, and on some properties of the antibody and its inhibitor.

* The following abbreviations will be employed throughout this paper: PVP, polyvinylpyrrolidone; ITP, idiopathic thrombocytopenic purpura; DLE, disseminated lupus erythematosus; PMN, polymorphonuclear leukocyte; TEPA, triethylene phosphoramide; PTC, plasma thromboplastin component deficiency; PNH, paroxysmal nocturnal hemoglobinuria; AHA, acquired hemolytic anemia.

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Methods and Materials

1. *Sera.*—A total of 400 sera, 350 from patients with varying hematologic disorders and 50 from presumably healthy medical students, was examined for leukoagglutinins. Employed in the tests were either freshly drawn or promptly frozen sera. In common with the findings of other observers, our experience showed that freezing apparently did not affect the agglutinin. All sera were Seitz-filtered to obtain maximum freedom from small particles to which leukocytes might adhere. Unless otherwise specified, all sera were heated at 56 C for one-half hour to inactivate complement and the thermolabile inhibitor of agglutinatoin.

2. *Leukocytes.*—Except in special instances, all leukocytes were obtained from presumably healthy donors who gave no history of transfusions. Immediately after venipuncture, 20 ml. of blood was defibrinated with glass beads. To four parts of defibrinated blood was added one part of 4%

polyvinylpyrrolidone (PVP).† This mixture was allowed to sediment for approximately one hour at 37 C. The exact time varied with individual sedimentation rates. The ideal sedimentation period yielded a minimum of erythrocytes with a maximum of leukocytes in the upper portion of the tube. Too long a sedimentation period would reduce the number of leukocytes below the optimum for agglutination procedures. Sufficiently high numbers of white blood cells should be obtained so that the suspension could be diluted with inactivated compatible serum to the optimum of 2500 to 3500 per cubic millimeter, thereby reducing the number of erythrocytes proportionally. Leukocyte suspensions were obtained by first withdrawing the leukocyte-containing supernatant PVP-serum. The leukocytes were counted, and then the suspension was diluted to the optimum number of leukocytes by the addition of one of two diluents. The diluent employed in early studies was the cell-free supernatant obtained by centrifuging the remaining PVP-blood mixture. Because of the inhibitory action of the PVP-serum mixture, inactivated ABO blood-group serum, homologous to both donors of leukocytes and test serum, was substituted. Leukocyte suspensions, kept in the refrigerator prior to use, were used only on the day of preparation.

3. *Sedimenting Agent.*—PVP was utilized throughout these studies to enhance sedimentation. A 4% PVP solution in isotonic saline was prepared by warming at 37 C to hasten solution. This mixture was approximately at pH 4 and was adjusted with 0.1 N NaOH to pH 7.2 before sterilization. The reagent could be kept indefinitely at 6 C.

4. *Agglutination Test.*—In the survey for leukoagglutinins, three different amounts of test serum were routinely employed. Each of the three amounts, 0.15 ml., 0.1 ml., and 0.05 ml. of test serum, was mixed with 0.05 ml. of leukocyte suspension in a Kahn test tube and incubated for a minimum of one hour at 37 C. Prolonged incubation for more than two hours tended to give false-positive results. Leukocytes from homologous ABO blood-group donors were mixed with their respective group sera to avoid adherence of the leukocytes to agglutinated clumps of red cells or stroma. After incubation any erythrocytes in the mixture were lysed by the addition of 0.1 ml. of 2% acetic acid. A drop of the settled leukocytes was withdrawn from the bottom of the test tube for microscopic examination (×100). Centrifugation of the mixture did not markedly enhance agglutination and was not used in this work. In surveying sera for leukoagglutinins, at least two different donors for white cells were used routinely. Some of the positive sera were tested with many different leukocytes.

5. *Agglutination Titers.*—Serial doubling dilutions of test serum were prepared, using inactivated homologous ABO group serum as diluent. Isotonic saline was an unsatisfactory diluent in that it induced spontaneous agglutination. To each dilution of serum was added 0.05 ml. of leukocyte suspension. The mixture was treated as described in the technique of the agglutination test.

† The PVP was donated by the Commercial Development Department of General Aniline and Film Corporation, 435 Hudson St., New York 14.

Results

Distribution of Leukoagglutinins in Certain Diseases.—The sera from 400 individual subjects were examined for the presence of agglutinins for white blood cells. In the group were 50 presumably healthy medical students, while the rest were patients, most of whom had some hematologic problem. The majority had primary hematologic disease, and a few had secondary blood disorders. Leukoagglutinins were not found in the students. In the selected group with disease, 38 of 350 patients, over 10%, were found to have leukoagglutinins (Table 1). The patients were studied for age incidence, sex difference, and blood group, with no significant correlation with any of these factors.

The anemias, the leukemias, the idiopathic thrombocytopenic purpuras (ITP), and the collagen diseases accounted for most of the patients with leukoagglutinins. An analysis

TABLE 1.—*Distribution of Leukoagglutinins in 350 Patients with Hematologic Diseases and 50 Normal Subjects*

Groups of Diseases Investigated	No. Patients Examined	No. Patients with Leuko-agglutinins
Anemia	94	21
Leukopenia	22	1
Idiopathic thrombocytopenic purpura	15	2
Miscellaneous purpuras	5	0
Polycythemia vera	9	0
Leukemia	77	10
Lymphoma	26	0
Myeloma	4	0
Malignant neoplasms	22	1
Collagen diseases	31	3
Coagulation disorders	7	0
Miscellaneous	38	0
Normals	50	0
Totals	400	38

TABLE 2.—*Distribution of Leukoagglutinins in Anemia*

Type of Anemia	No. Patients Examined	No. Patients with Leuko-agglutinins
Idiopathic AHA (Coombs+)	15	6
Chronic hemolytic anemia (Coombs −)	1	1
Erythroblastosis	1	0
Paroxysmal cold hemoglobinuria	1	0
Favism	1	0
Hypersplenism	3	0
Sickle	7	0
Sickle trait	3	0
Mediterranean trait	1	0
Spherocytosis	1	0
PNH	4	2
Aplastic anemia (idiopathic)	14	1
Aplastic anemia (drug-induced)	5	3
Hypoplastic anemia	2	0
Anemia of blood loss	2	2
Pernicious anemia	2	0
Myelofibrosis	3	2
Anemia in pregnancy	2	1
Anemia of liver disease	2	1
Pancytopenia	13	1
Undiagnosed anemia	11	1
Totals	94	21

of the various kinds of anemia in which leukoagglutinins were present is shown in Table 2. The occurrence of leukoagglutinins in the anemia of liver disease, in myelofibrosis, in refractory anemia in pregnancy, and in the blood-loss anemias associated with esophageal varices and hiatus hernia has not been previously reported. These antibodies for leukocytes were not detected in the congenital anemias that were examined. The in vitro demonstration of leukoagglutinins in the three presumably drug-induced aplastic anemias without the addition of the inciting agent is of interest. These were patients who had recovered. The inciting drugs were thought to be chloramphemnicol (Chloromycetin) in Patient 32, trimethadione (Tridione) or phenacemide (Phenurone) in Patient 196, and either quinacrine (Atabrine) or cyanide in patient 335 (Table 4). The etiology in Patient 147 was unknown, although the patient was followed in the hospital for three years. She died two and one-half months from the time the leukoagglutinin studies were first initiated. The white cell agglutinins were found in all the forms of leukemia (Table 3) except the very few cases of stem-cell type. In the total series only 1 patient with leukopenia and thrombopenia out of 22 cases of otherwise unclassified leukopenias and 1 case of neuroblastoma of 22 cases of malignant neoplasms had leukoagglutinins. Over half of the 31 patients with collagen diseases had disseminated lupus erythematosus (DLE); three of the latter had leukoagglutinins. Leukoagglutinins were absent in this series in the lymphomas, in polycythemia vera, in the miscellaneous purpuras, and in the coagulation disorders.

Relation of Leukopenia and/or Neutropenia to Occurrence of Leukoagglutinins.—Leukopenia (total leukocyte count less than 3500 per cubic millimeter and/or neutropenia (less than 50% PMN) did not occur in the patients with leukoagglutinins to the extent that would be anticipated from the experience of other workers.[3-8,14,16,18,20] Of the 36 patients for whom leukocyte counts were available and who possessed leukoagglutinins, 23, or 64%, were neither leukopenic nor neutropenic at the time of testing. One additional patient fluctuated from low or slightly depressed leukocyte counts to normal during the period when leukoagglutinins were found. One other patient with a decreased white cell count concomitantly received triethylene phosphoramide (TEPA). The inclusion of these two patients would make a total of 25, or 69%, who were not consistently leukopenic or neutropenic at the time of testing (Table 4). Examination of the over-all history of the patients' leukocyte counts showed that 44%, or 16 of 36, were never leukopenic nor neutropenic.

TABLE 3.—*Distribution of Leukoagglutinins in Leukemia*

Type of Leukemia	No. Patients Examined	No. Patients with Leuko-agglutinins
Acute monocytic	10	3
Acute lymphocytic	22	2
Chronic lymphocytic	22	2
Acute granulocytic	8	2
Chronic granulocytic	12	1
Stem cell	3	0
Totals	77	10

TABLE 4.—*Patients with Leukoagglutinins* *

Patient	Disease	Antibodies					No. Transfusions Before 1st Leukoagglutinin Test	White Blood Cells		Remarks
		Coombs Test	Leuko-agglutinin Titers	L.E. Test	Platelet Isoagglutinins	Rh Antibodies		History	At Test Time	
3	Ac. aleuk. mono. leuk.	–	+				17	↓P	↓LP	Received 6-MP; died
33	Ac. mono. leuk.	–	1:1-1:2	NP		–	29	↓LP	↓LP	Received 6-MP, decreased WBC, neither N nor L during remission from cortisone; died
216	Ac. aleuk. mono. leuk. and AHA	+	1:4			+	4	↓L	N	Never neutropenic; aleukemic disease; no chemotherapeutic agents; died
48	Ac. aleuk. lymph. leuk.	–	1:2-1:4			–	12	↓L	↓L	Leukopenia at time of test due to 6-MP; died
64	Ac. lymph. leuk.	–	1:2-1:256	–		–	18	↓P	↓LP	Received 6-MP, 6-CH_3MP, O-diazoacetyl-L-serine (Azaserine), 6-chloropurine, 6-mercapto-2 amino-purine (Thioguanine) when WBC low
29	Chr. lymph. leuk.	–	1:4-1:64	–		–	18	↓P	↓LP	Received 6-MP and x-ray when WBC low
276	Chr. lymph. leuk.	–	+			–	53	↓P	↓P	Received triethylenemelamine (TEM)
165	Ac. gran. leuk.	–	1:4-1:32			–	65	N	↓LP	No chemotherapeutic agents; transitory leuko- and neutropenia; died
282	Ac. gran. leuk.	–	1:2-1:128			–	14	N	N	Received 6-MP; no drop in WBC; died
158	Chr. gran. leuk.	–	1:1	–		–	0	L↑	N	Received busulfan (Myleran); agglutinin disappeared after several months
147	Apl. anemia	–	1:16-1:32	NP		–	120	↓LP to N	↓L	Cause of aplastic anemia unknown; died
37	Apl. anemia	–	+				50	↓L	N	Inciting drug chloramphenicol; recovered
196	Apl. anemia	–	1:2-1:16			–	100	↓LP	N	Inciting drug either trimethadione or phenacemide; recovered
335	Apl. anemia	–	1:4			–	148	↓LP	L↑	Inciting drug either quinacrine or cyanide; recovered
179	Myelofibrosis	–	1:4-1:256		+	–	47	↓L	↓L	Agglutinin demonstrable before and after splenectomy
311	Myelofibrosis	– (2+ alb. test)	+			–	8		L↑	Ruptured spleen at test time; died
152	Chr. hem. anemia	–	1:1-1:128			–	109	↓L	↓L to N	Number of leukocytes became normal after splenectomy
215	AHA	1:640	1:8				3	N	N	Died
212	AHA	1:2,560	1:16			–	10	N	L↑	
217	AHA	+	+							Data on transfusions and number of leukocytes not available

TABLE 4.—*Patients with Leukoagglutinins**—Continued

Patient	Disease	Antibodies					No. Transfusions Before 1st Leukoagglutinin Test	White Blood Cells		Remarks
		Coombs Test	Leuko-agglutinin Titers	L.E. Test	Platelet Isoagglu-tinins	Rh Anti-bodies		History	At Test Time	
218	AHA	1:160	1:2-1:16				5	N	L↑	
249	AHA	1:1,280	+			−	2	L↑	N	Leukoagglutinin developed after transfusion therapy
11	AHA and ITP	1:640	1:2				0	↓ Slight L to N	N	Agglutinin disappeared after splenectomy
372	An. of liver dis.	−	1:2-1:16			−	40		↓L	
321	Refractory an. in pregnancy	−	1:4-1:8			−	0	N	L↑	Agglutinin disappeared post-partum
94	Pancytopenia	− (4+ alb. test)	1:4			−	18	N	N	Leukoagglutinin developed after increase in transfusions; died
316	Esoph. varices	−	1:256-1:512			−	17	L↑	L↑	
347	Hiatus hernia	−	1:4			−	Few	N	N	
267	Undiag. anemia	−	1:4-1:128			−	4	N	N	Agglutinin not demonstrable in later sample
15	ITP	−	1:16			+				Data on transfusions and number of leukocytes not available; died
43	ITP	−	1:8-1:256	−	+	−	150	L↑	N to L↑	Died
241	Thrombo. and leukopenia	−	+				0	↓LP	N	Recovered; disease very transitory
210	DLE	−	1:8	+		−	2	N	L↑	Died
214	DLE	1:80	1:4	+		+	12	N	N	
213	DLE	1:320	+	+			10	N	L↑	
10	PNH	1:160	1:4-1:16		+	−	50	↓LP	N	WBC and % PMN increased during bishydroxycoumarin (Dicumarol) treatment.
16	PNH	−	1:2-1:128			−	28	↓LP	↓LP	Died
256	Neuroblastoma	−	1:64-1:512			−	13	L↑	↓L	Received TEPA, chlorambucil (CB 1348), in early stages of disease; died

* Explanations of abbreviations: NP indicates nucleophagocytosis; ↓, decreased; P, polymorphonuclear cells; L, leukocytes; N, normal leukocyte count and normal distribution; ↑, increased; 6-MP, 6-mercaptopurine; 6-CH_3MP, 6-methylmercaptopurine.

In many instances the neutropenia and leukopenia were confined to certain of the disease entities, e. g., the monocytic and lymphocytic leukemias, the aplastic anemias, and the myelofibroses. Repeated tests for leukoagglutinins in patients with cyclic neutropenia and agranulocytosis were consistently negative. Leukopenia or neutropenia were not characteristic of the majority of the other diseases. The patients with leukemia possessing leukoagglutinins had all (with one exception) received chemotherapeutic agents which during treatment tend to reduce the leukocyte count. This treatment of itself did not appear to be responsible for the development of leukoagglutinins, for 24 patients whose leukocyte count was depressed from drug treatment at the time of testing did not have leukoagglutinins in their sera. In this drug-treated group, the patients without leukoagglutinins who were leukopenic had had few if any transfusions. The highest number of transfusions in this latter group was 11.

Relation of Transfusions to Leukoagglutinins

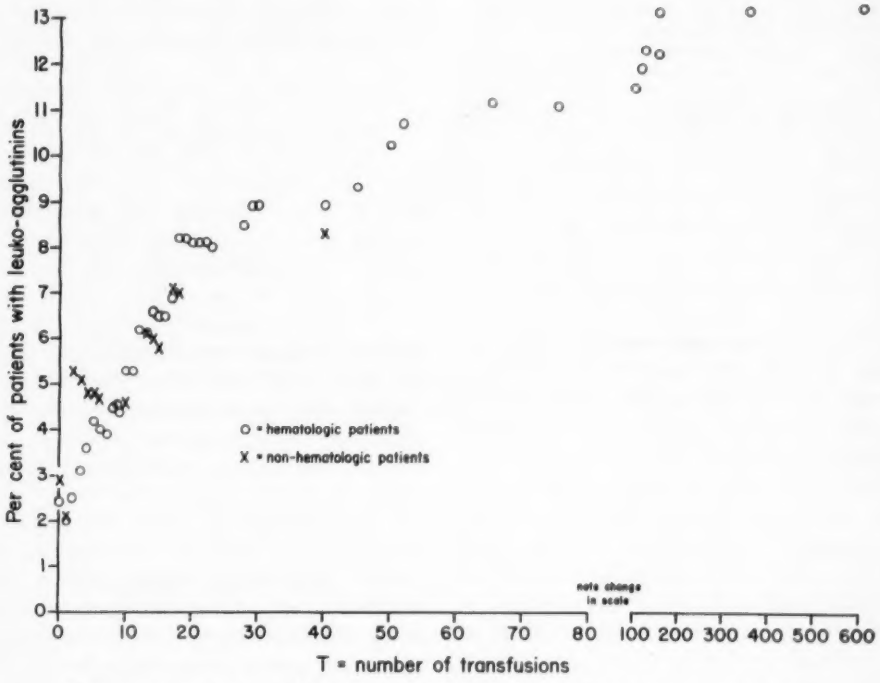
A. Numbers of Transfusions in Patients with Leukoagglutinins.—The occurrence of multiple transfusions in almost all patients in whom leukoagglutinins were found has been even a more striking phenomenon in our findings than in those of other investigators.[6,9,12,14-17,20] In the literature, there are very few reports of these agglutinins in the absence of transfusions.[8,12,18]

In the 38 patients reported in Table 4, the number of transfusions prior to testing for leukoagglutinins ranged from 0-150. The majority, 90%, had had transfusions; only four patients gave no history of transfusions. Examination of the number of transfusions per patient demonstrated that the fewest were among the patients with anemias and with disseminated lupus erythematosus (DLE). A greater number of transfusions was found in paroxysmal nocturnal hemoglobinuria (PNH) and the leukemias. The largest number of transfusions occurred in the aplastic anemias. Exceptions or overlapping of these rough groupings were common.

Should one assume that transfusions are the stimulation responsible for the development of leukoagglutinins, it must be noted that not all patients who have received multiple transfusions produce these agglutinins. While the number of transfusions appeared to be a determining factor, they were not the sole factor. Table 5 displays for two series of patients the number with and without leukoagglutinins classified by the number of blood transfusions received prior to the first test. In this Table, the patients were divided into two groups, which were designated "hematologic" and "nonhematologic." "Hematologic" included all those in whom the primary tissue involved in the disease process appeared to be the blood or the blood-forming tissue, e. g., leukemia, ITP, multiple myeloma, and AHA. "Nonhematologic" included all other patients who may or may not have had a secondary hematologic problem but in whom the primary disorder was not the blood or the blood-forming tissue, e. g., esophageal

TABLE 5.—*Number of Transfusions in Patients Tested for Leukoagglutinins*

Hematologic Series			Nonhematologic Series		
No. Transfusions	No. Patients with Agglutinins	No. Patients Without Agglutinins	No. Transfusions	No. Patients with Agglutinins	No. Patients Without Agglutinins
0	2	80	0	1	34
1-5	4	58	1-5	2	26
6-10	3	22	6-10	0	2
11-20	7	21	11-20	2	4
21-30	2	3	21-30	0	0
31-50	3	2	31-50	1	0
More than 50	7	4	More than 50	0	0
Total	28	190	Total	6	66


Per cent of patients with leuko-agglutinins
O = hematologic patients
X = non-hematologic patients
note change in scale
T = number of transfusions

Per cent of patients with leukoagglutinins who received T or fewer transfusions.

varices, peptic ulcer, and carcinoma. A few patients in whom the diagnosis was not clearly established were omitted from the table. Study of these data suggests that leukoagglutinins occur more frequently among subjects who have had many transfusions. In fact, there appears to be an increasing trend relating the likelihood of positive leukoagglutinin test to the number of transfusions received. These suggestions are less pronounced in the nonhematologic series, perhaps due in part to the paucity of cases in this series.

This increasing trend can also be seen in the Figure, where the abscissa represents the number of transfusions a patient has ever had, and the height of a curve at point T denotes the percentage of patients with leukoagglutinins among those who have had T or fewer transfusions. The upward slopes indicate that patients with many transfusions include a higher proportion of patients with leukoagglutinins.‡

To the ungrouped data (i. e., using the exact number of transfusions for each patient) one can apply standard rank-order statistical methods to (1) express the strength of association between the two variables, number of transfusions, and occurrence of leukoagglutinins and (2) test the significance of this observed relationship. The results are shown as follows, where τ is a measure of strength of relationship, similar to a correlation coefficient:[24] Hematologic, $\tau = 0.36$ ($N = 218$); nonhematologic, $\tau = 0.26$ ($N = 72$). The first of these is highly significant, exceeding five times its standard error. The second is about

‡ The statistical analysis was prepared by Dr. Lincoln E. Moses, Associate Professor of Statistics, Departments of Preventive Medicine and Statistics, Stanford University School of Medicine.

TABLE 6.—*Number of Transfusions in Patients with Leukemia Prior to Testing for Leukoagglutinins*

No. Transfusions	No. Patients with Agglutinins	No. Patients Without Agglutinins
0	1	29
1-5	1	19
6-10	0	11
11-20	5	7
21-30	1	0
31-50	0	1
More than 50	2	0
Totals	10	67

2.6 times its standard error and thus significant at the 1% level. There are insufficient data to enforce the conclusion that there is a stronger association in the hematologic subjects.

It is interesting to inquire as to whether the relationship between occurrence of leukoagglutinin and number of transfusions is a result of a difference between "no transfusions" and "some transfusions." To examine this matter, all untransfused patients were left out and the data reanalyzed. The results are as follows: Hematologic, $r=0.34$ ($N=136$); nonhematologic, $r=0.29$ ($N=37$). Again the result for the hematologic series is highly significant; in the other series it is about 1.96 times its standard error. It is not possible to demonstrate a difference between the two series with regard to the strength of the relationship.§

It can be concluded that leukoagglutinin formation occurs more commonly among patients who have been frequently transfused. This conclusion is very strongly indicated by a series of 218 hematologic patients and somewhat less strongly by a series of 72 nonhematologic patients.

Specifically, the number of transfusions in patients with and without leukoagglutinins among those with leukemia and DLE are shown in Tables 6, 7, and 8. In these smaller series with a specific disease, the same increasing trend of occurrence of leukoagglutinins with multiple transfusions is also suggested.

B. Patients with Agglutinins But No History of Transfusions.—Careful study of the patients with leukoagglutinins in the absence of history of transfusions is essential to an understanding of the role of leukoagglutinins per se as well as to the possible role of transfusions in their production. The salient features on the agglutinins of these four patients up to the time of pub-

§ This coefficient and test of significance associated with it are explained and justified in M. G. Kendall.[21]

TABLE 7.—*Relation of Number of Transfusions to Kind of Leukemia in Cases With and Without Leukoagglutinins*

No. Transfusions	Ac. Lymphocytic		Chr. Lymphocytic		Ac. Granulocytic		Chr. Granulocytic		Ac. Monocytic		Blast	
	+	−	+	−	+	−	+	−	+	−	+	−
0		3		13		2	1*	7		3		1
1		3		1								
2		6†								1		
3						1			1‡	1		1
4		3										
5		1				1						
6						1		1				
7										1		
8		1										
9				1				1				
10		2		1						1		1
11				1				1				
12	1	1				1						
13												
14					1							
15												
16				1								
17				1					1			
18	1		1									
20				1								
29									1			
40							1					
53			1									
65					1							

* This agglutinin was not demonstrable several months after the first test.
† One case had positive Coombs but still negative for WBC agglutinins.
‡ With AHA and positive Coombs.

TABLE 8.—*Relation of Transfusions to Occurrence of Leukoagglutinins in Disseminated Lupus Erythematosus with L. E. Cells*

No. Transfusions	No. Patients with Agglutinins	No. Patients Without Agglutinins
0	0	10
1	0	2
2	1	0
6	0	1
10	1	0
12	1	0

lication follows. Patient 158, with chronic myelogenous leukemia, possessed a leukoagglutinin of limited specificity. Serum was obtained from this patient on four occasions over a period of 10 months. The first sample agglutinated the leukocytes of three of four donors; the next sample, drawn 2 months later, agglutinated the leukocytes of two of four donors; the third sample, drawn at 7 months, and the fourth sample, drawn at 10 months, both failed to agglutinate the leukocytes of two donors. Patient 11, with idiopathic AHA and thrombocytopenia, had agglutinins prior to, but not four to six days after, splenectomy. Two units of blood was administered at the time of splenectomy. Patient 321, with a refractory anemia in pregnancy, was tested on four occasions, twice prepartum and twice postpartum. On the first two occasions the leukoagglutinin was present in a titer of 1:8. The postpartum tests were negative. Patient 241 was tested on two occasions. The first sample agglutinated the leukocytes of three donors, but the second sample, drawn 11 months later, failed to agglutinate any leukocytes. These four patients with leukoagglutinins in the absence of transfusions will be carefully followed.

C. Development and Disappearance of Leukoagglutinins During Transfusion therapy.—The foregoing data, while suggestive of some correlation between transfusions and the development of leukoagglutinins, obviously do not establish the origin of leukoagglutinins. However, there are some curious bits of evidence in the cases which were studied in this laboratory, supporting the idea that the leukoagglutinins may in some cases be the result of transfusion. Several patients, two with AHA, one with a refractory anemia, and one with chronic lymphocytic leukemia, developed leukoagglutinins during the course of treatment which included transfusion therapy. Patient 249, with AHA, developed leukoagglutinins 10 days after receiving two units of blood. This time interval is consonant with the usual time lapse for antibody production. Another patient with AHA, Patient 215, was found to have leukoagglutinins in a sample of serum drawn seven months after transfusions. This patient's serum drawn prior to transfusion did not contain leukoagglutinins. Patient 94, with a pancytopenia, had no agglutinins following 14 transfusions administered over a period of many months. But additional transfusions three months after the preceding series of 14 were followed by the development of leukoagglutinins as well as a positive albumin test for red cell antibodies. The patient with chronic lymphocytic leukemia, Patient 29, was tested after three transfusions and found not to have leukoagglutinins. Eleven months later, after 18 additional transfusions, this patient possessed a leukoagglutinin titer of 1:4. One must consider, of course, that the presence of leukoagglutinins after transfusions in these four patients might also be interpreted as a natural development of the inherent disease, or as a result of other therapy rather than the direct result of transfusions.‖

In contrast to the four patients who developed agglutinins after transfusion, Patient 11, referred to earlier, had an agglutinin which disappeared after transfusions. Several factors complicated any interpretation of this patient. The effect of splenectomy, the short time interval after transfusion, and his positive serologic test for

‖ Since this manuscript was prepared, six more patients whose first samples tested had no agglutinins were found to have leukoagglutinins following additional transfusions. These were in the patients with acute myelogenous leukemia, acute lymphatic leukemia, PTC deficiency, and aplastic anemia.

TABLE 9.—*Time Lapse from Transfusion to Leukoagglutinin Test*

Patient	Diagnosis	No. Transfusions	Titer	Time Since Last Transfusion
311	Myelofibrosis	8	1:1	3 yr.
212	Acquired hemolytic anemia	10	1:16	3 yr.
335	Aplastic anemia	148	1:4	5 yr.
215	Acquired hemolytic anemia	3+	1:8	7 mo.
267*	Undiagnosed anemia	4	1:16	9 mo.

* One month following last positive demonstration of agglutinins none was detectable in this patient.

syphilis (which might have been a biologic false-positive since there was no other evidence of syphilis) may all have bearing on the differing result. In Patient 267, who had had four transfusions, the leukoagglutinins, which were demonstrable on three occasions during one month, disappeared three weeks later. The leukoagglutinin of Patient 321, who received two units of blood at delivery, also disappeared after transfusion.

D. Time Lapse from Transfusion to Leukoagglutinin Test.—Five of the patients with leukoagglutinins had not been given transfusions in the recent past. The time lapse since their last transfusion along with the number of transfusions administered can be seen in Table 9. One patient had not had a transfusion for five years, two others had had none for three years, and the last two had not received blood in over six months. With the exception of the patient with aplastic anemia and 148 transfusions, the number of administrations was not large in the other four patients. If leukoagglutinins are assumed to be caused by the transfusions, then the data of Table 9 would tend to demonstrate that such agglutinins might persist for a considerable time without restimulation and without apparent relation to the total number of transfusions. Unfortunately, the time of development of the leukoagglutinin was not demonstrated in these cases, and the etiological speculation is tenuous at best. Follow-up studies now in progress on patients who developed agglutinins during treatment may provide more clarifying data on the persistence of leukoagglutinins after transfusion.

E. Effect of Transfusions on Leukoagglutinin Titers.—It was possible to follow six patients with leukoagglutinin titers after additional transfusions. Although some titers fluctuated during this period of transfusions, a clear-cut anamnestic response could not be demonstrated.

F. Transfusion Reactions in Patients with Leukoagglutinins.—In this series, 13 of the 32 patients on whom records were available appeared to have transfusion reactions. Criteria for a reaction were shock, chill, or temperature rise to 39 C or higher. DeGowin, Hardin, and Alsever (1949) reported that the incidence for all types of reactions was 3.4% in a series of 5386 transfusions. Reactions with chills and fever were only 1.8%.[25]

Nature of the Antibody

Relationship of Leukoagglutinin to Other Antibodies.—Since the humoral factor stimulating the production of L. E. cells and an agglutinin for leukocytes were found at the same time in the sera of some patients with DLE, the problem of the identity or difference of the two factors arose. Nine patients, other than those with DLE, in whom leukoagglutinins were present, were studied for the presence of L. E. cells. In this group no L. E. cells were found. Occasionally tart cells and erythrophagocytosis were observed.

The existence of a positive Coombs test or other evidence of red cell sensitization in a patient may or may not coincide with the presence of a leukoagglutinin. In 15 patients with AHA (Coombs test positive), nine patients were found to be without leukoag-

glutinins (Table 2); a patient with acute lymphocytic leukemia and superimposed AHA (Coombs test positive) had no demonstrable leukoagglutinins (Table 7). The concomitant occurrence of leukoagglutinins and antibodies for red cells (Coombs test or albumin test), or platelet agglutinins, or the L. E. factor, or Rh antibodies may be seen in Table 4. Among the 38 leukoagglutinating sera, three were found to have Rh antibodies. Patient 216, acute monocytic leukemia, had a panagglutinin with an incomplete anti-D titer 1:16, anti-C 1:8, anti-E 1:8, and anti-cde 1:32; Patient 15, ITP, had a titer of incomplete anti-D 1:128; Patient 214, DLE, had a titer of incomplete anti-D of 1:16. The serum of Patient 15 was absorbed with Group O, Rh-positive (D) erythrocytes. After complete absorption of the anti-D component, the titer of the leukoagglutinin was unaltered.

Types of Leukocytes Agglutinated—Routinely, the test leukocytes were drawn from healthy donors with normal differential counts and no history of transfusion. Most of the leukoagglutinins were active against almost all donor leukocytes. One patient's serum was tested with leukocytes from 20 donors, with all donors' cells being agglutinated. Half of the leukoagglutinating sera were tested against more than six leukocyte donors; others were tested against a minimum of two donors' leukocytes. In addition to the use of leukocytes of presumably healthy donors, some of the leukoagglutinating sera were also tested against cells from donors with varying diseases, e. g., leukocytes drawn from patients with DLE, aplastic anemia, chronic myelogenous leukemia, one with 40% basophilic cells, acute and chronic lymphocytic leukemia, PNH, pancytopenia, and ITP. All of the test white blood cells from patients with hematologic disease were agglutinated except those from two donors with aplastic anemia which were agglutinated by only one of the leukoagglutinating sera.

The white blood cells from patients with leukoagglutinins were readily agglutinated by other leukoagglutinating sera. No patient's serum could be clearly demonstrated to agglutinate his own white blood cells. The agglutinable leukocytes were obtained from Patient 16, PNH; Patient 43, ITP; Patient 94, pancytopenia, and Patient 64, acquired lymphocytic leukemia. The last-mentioned patient consistently maintained a 90% to 99% lymphocyte population. From these trials it would appear that the cell types of patients with leukoagglutinins so far employed were agglutinable. Suspensions of predominantly blast cells which had been reported inagglutinable were not tested.

Occasionally, leukocytes obtained for testing sera appeared to be agglutinated by almost all sera, including series of known negative sera. This situation was uncommon, for only three examples were observed in the course of more than a year's work. Perhaps if white blood cells from patients were utilized, more of these would have been encountered.

Precipitin Tests.—An initial trial with a soluble antigen for precipitin tests was unsuccessful. Washed leukocytes suspended in distilled water were repeatedly frozen and thawed, following which the mixture was centrifuged. The resultant slightly turbid supernatant was employed as antigen. Known leukoagglutinating sera failed to yield any precipitate. The production of a precipitating antigen would be helpful because the instability of leukocyte suspensions employed in the agglutination technique requires daily collection. This is a deterrent to the standardization of the agglutination technique and limits the quantity of tests that may be carried out at one time. Such an antigen could be prepared from pooled leukocytes which might provide all the possible leukocyte antigens.

Autoagglutinins for Leukocytes.—The finding of an autoantibody in patients with agglutinins would be critical for the demonstration of an immunoleukopenia. Whenever possible, the leukoagglutinating serum

was tested against autologous leukocytes. The patients who were tested (Patient 43, ITP; Patient 10, PNH; Patient 64, acute lymphocytic leukemia; Patient 158, chronic granulocytic leukemia) were essentially negative. On one occasion, the serum of Patient 43 appeared weakly positive, but this could have been explained by the large number of leukocytes used in the test sample (drawn during a period of leukocytosis). This patient had had more than 200 transfusions when weak autoagglutination was observed. Several patients (aplastic anemia, chronic myelogenous leukemia, and DLE), as well as 15 normal persons, none of whose sera contained isoleukoagglutinins, were also tested for autoagglutinins. All these were negative, except one case of DLE, who had a weekly positive test similar to that of Patient 43, ITP. By the present technique, an autoagglutinin could not clearly be demonstrated in any patient who was studied.

Electrophoresis.—Paper electrophoretic patterns of the leukoagglutinating sera were in the main normal as to distribution of serum proteins. A few showed an increase in the γ-globulin component. One aplastic anemia patient, Patient 147, who developed agammaglobulinemia during the terminal phase, maintained a leukoagglutinin titer throughout the course of the disease. Abnormal proteins found in sera, such as cryoglobulins or the patterns of multiple myeloma, did not of themselves induce leukoagglutination.¶

Temperature Requirements.—The leukoagglutinins were originally demonstrated at 37 C and therefore were assumed to be agglutinins of the warm type. Several sera, tested at varying temperatures, 4, 20, and 37 C, failed to act at any temperature but 37 C. The serum of Patient 43, ITP, was active at 20 C as well as at 37 C, which might be accounted for either by the high titer of the serum or by a different type of antibody. The tendency for leukocytes to agglutinate spontaneously or to disintegrate on prolonged standing prevented trials at intervals longer than two hours. Increased time of incubation might yield positive agglutination at lower temperatures if a stable antigen were available.

The Inhibitor.—The nature of the inhibitor of leukoagglutinins present in sera was partially explored. The inhibitor could not be dialyzed out into saline from the serum, suggesting that it may be protein or of large molecular weight. One-half hour incubation of serum at 56 C completely inactivated the inhibitor, confirming the thermolability ascribed to it.[6] Cohn's plasma fractions were reconstituted and tested for inhibiting action. None of the fractions had any inhibiting effect. The relatively drastic procedure for preparation of these fractions may well account for the loss. Normal fresh serum (containing inhibitor) will inhibit the agglutination of white blood cells by leukoagglutinating serum when both are added to the cells simultaneously in the ratio of two parts of fresh serum to one of agglutinating serum. The serum inhibitor of leukoagglutinins did not block agglutination in the manner that incomplete Rh antibodies block the action of a saline agglutinin. That is, when agglutinating serum containing inhibitor (i. e., not inactivated) was incubated with white blood cells for an hour, then the active serum decanted, and inactivated agglutinating serum added, the cells were agglutinated. It was not possible to demonstrate whether or not inhibitor could be washed off from leukocytes. The washing of leukocytes previously treated with inhibitor or of untreated cells rendered them inagglutinable. When six parts of inhibitor were added to one part of agglutinated cells and incubated at 37 C for 24 hours, the inhibitor did not act as a reverser of leukoagglutination.

Comment

The significance of the finding of leukoagglutinins in human serum has been and

¶ Later, a patient with multiple myeloma who had had 31 transfusions was found to have a leukoagglutinin.

continues to be the primary question under consideration. Secondarily, the particular nature of the leukoagglutinating antibody deserves attention. The discussion of the significance of leukoagglutinins will center around whether or not leukoagglutinins are (1) autoantibodies, (2) primarily associated with leukopenia, (3) artificially induced isoantibodies for leukocytes and the consequence of transfusions, and, finally, (4) related to some transfusion reactions.

At the present time, the majority of leukoagglutinins cannot be assumed to be autoantibodies responsible for immunoleukopenias or immunoneutropenias. First, the majority of reported leukoagglutinins have not been shown to react with leukocytes of the same patient, and, therefore, one prerequisite for autoactivity has not been fulfilled. Furthermore, the demonstration of a shortened life span of the leukocyte which has been sensitized by an autoantibody would be desirable for the establishment of an immunoleukopenia as a distinct entity. In two immunohematologic disorders, idiopathic AHA and ITP, an autoactivity has been demonstrated in the form of antibody attached to the patient's erythrocytes or platelets, as well as in the form of antibody in the patient's serum, which has identical specificity. In AHA, erythrocytes sensitized by this antibody may have a shortened life span during the acute phase. In these latter immunodisorders, artificially induced isoagglutinins, apparently the consequence of transfusions in many instances and reacting only with other donor cells, may exist together with autoagglutinins in a given serum. The behavior of the leukoagglutinin resembles that of an isoantibody, for its activity is directed toward leukocytes, not from the autologous, but from homologous, ABO blood group donors. A leukoagglutinin in a patient who has received transfusions cannot be considered an autoagglutinin until proof of its specificity for the patient's leukocytes has been demonstrated. Scattered reports of a few instances of autoleukoagglutinins are encouraging, but not all are completely convincing. Perhaps the demonstration of more may follow with the development of improved techniques. Aside from the report of Moeschlin and Wagner [1,2] of an autoagglutinin present when aminopyrine had been recently administered, the other reports refer in the main to relatively weak autoagglutination of leukocytes. As late as December, 1954, Dausset [8] stated that it was not possible to demonstrate autoleukoagglutinins in 26 patients with leukoagglutinins. One patient with chronic pancytopenia in his series gave evidence of a tendency to autoagglutination independent of the medium in which the leukocytes were suspended. Marchal, Duhamel, Dausset, and Libeskind [9] described doubtful autoleukoagglutination in a patient with Hodgkin's disease. Evans and Parkinson [26] observed autoleukoagglutination in patients with DLE. Occasionally it has seemed that weak autoagglutination took place between patient's cells and serum in our work, but this experience could not be consistently duplicated.

One instance of weak agglutination was observed during a period of marked leukocytosis in Patient 43, who had had more than 200 transfusions. Factors other than true autoagglutination may have operated here. Dausset [8] has offered the hypothesis that transfusions may widen the range of action of a leukoagglutinin which was originally "auto" in character. It would seem, however, in the patient presented here that the reverse may be the case. The additional transfusions could have sufficiently widened the spectrum of activity of the isoleukoagglutinin so that a weak autoagglutination was possible. Moeschlin and Schmid's studies [27] on leukocyte agglutination suggest still another possibility for explaining the weak autoagglutination. They noted an increased "leukocyte-stickiness" resulting from infections and inflammatory reactions.

To date, the main method for the demonstration of antibodies for leukocytes, used almost exclusively by some investigators, has been in essence a test for isoleukoag-

glutinins. This method itself, while providing useful new information, requires considerable refinement. A Coombs test for leukocyte antibody attached to the cell does not appear to have been thoroughly explored; only brief reports of negative results have been published.[6,8,12] Initial trials with the precipitin test were not successful here or in the hands of some other workers. Recently, however, Seligmann, Grabar, and Bernard [28] have described a precipitin test with leukocyte lysates which gave positive ring tests in eight patients suffering from acute leukemia. Three of these nonleukopenic patients gave no history of transfusion, which led the authors to think that autoantibodies and not isoantibodies were operative. It must be noted, though, that the lysate was prepared from normal leukocytes rather than the patient's leukocytes. The demonstration with lysates of the patient's leukocytes would have been particularly pertinent to the question of autoactivity. It was not clear whether leukoagglutinins were also found in these sera, although a search for them was conducted. Results on tests for leukoagglutinins and leukoprecipitins were said not to agree.

A potent argument for the existence of an immunoleukopenia, aside from the demonstration of autoactivity, would be the finding of leukoagglutinins in the absence of a history of transfusion. This too has not been sufficiently common to clarify the situation. Miescher [18] reported one such case, and Dausset [8] spoke of three more, but detailed data were not presented on these latter patients. Goudsmit and van Loghem [12] also reported three patients with leukoagglutinins in the absence of a history of transfusions. One suffered from AHA, another from DLE, and the last from paroxysmal cold hemoglobinuria. Doubt was cast on the validity of the findings when the last workers later reported the need to recheck their patient's sera because of bacterial contamination. The four patients in the series of 38 presented here do not as yet clearly substantiate the continued existence of leukoagglutinins in the absence of transfusions. In the case of Patient 158, chronic myelogenous leukemia, the leukoagglutinin was demonstrated in the first sample to act on three of four different leukocyte suspensions—strongly on only one. Seven weeks later, another serum sample reacted very weakly with three out of four different leukocyte suspensions. Serum samples, obtained six and eight months after the first one, failed to agglutinate any of three different leukocyte suspensions. It is not characteristic of the isoleukoagglutinin to disappear from the serum of patients who have had transfusions. The first sample of serum of Patient 321, refractory anemia during pregnancy, was obtained two months prepartum and agglutinated two different suspensions of leukocytes whose red cells were Group A Rh-positive, but failed to agglutinate the leukocytes of Group A Rh-negative blood. The second sample of serum, obtained one week prepartum, acted in the same way. On the day of delivery the patient received 1 pt. of blood. A third sample of blood, obtained five weeks post partum, and a further sample, five months post partum, failed to agglutinate leukocytes from either an Rh-positive or an Rh-negative donor. In the case of Patient 11, ITP, I am not certain of the lack of transfusions in the medical history, and the patient has not as yet been available for a recent recheck. Patient 241, transitory leukopenia and thrombopenia, was tested on two occasions. Only the first sample agglutinated leukocyte suspensions; the second had no demonstrable leukoagglutinin. Insofar as the patients with no transfusion history are concerned, they have been insufficiently studied; these leukoagglutinins are aberrant from the usual in their behavior. The work of Moeschlin and Schmid [27] may have some bearing on interpretation of findings, such as in Patient 321. From their work on leukocyte agglutination in serum of compatible and incompatible blood groups, they proposed that apart from specific agglutinins, true agglutination is prob-

ably induced by the increase of normally present protein components that occur in certain pathologic conditions. So far, our experience with sera containing cryoglobulins and sera from patients with multiple myeloma does not support this thesis. The theoretical possibility exists that evidence establishing an immunoleukopenia may very well be obtained as new methods for the detection of such a disorder are applied. Standardized methods for determining the rates of production and destruction of leukocytes comparable to those for erythrocytes are required. At this time, however, it would be wise to exert caution in the discussion of leukoagglutinins by emphasizing the iso rather than the auto character of the serum antibody which has stimulated such renewed interest in the last few years.

The distribution of the isoleukoagglutinin in varying disorders has widened with each succeeding report in this field.[1,2,7,8,12,14] In this paper, additional diseases not previously reported were shown to be associated with isoleukoagglutinins. These are the anemia of liver disease, a refractory anemia during pregnancy, myelofibrosis, neuroblastoma, and the blood loss anemias of esophageal varices and hiatus hernia. The frequency of isoleukoagglutinins, more than 10%, coupled with the distribution in quite unrelated disease states often without leukopenia, would immediately suggest that other possible common denominators than an immunoleukopenia ought to be considered in explaining the significance of the leukoagglutinin in human sera. Neither leukopenia nor neutropenia occurred in a large number of the patients with isoleukoagglutinins presented in this paper. Among these patients, there were 42% who were neither leukopenic nor neutropenic throughout their known medical history. At the time of serum collection, 69% of the series presented here were neither leukopenic nor neutropenic. These results are quite at variance with those of Dausset,[8] who found 85% of his series of patients with leukoagglutinins to be either leukopenic or neutropenic. It would appear that Dausset primarily searched for these antibodies in leukopenic persons.

The contributions of Dausset and others on the distribution of leukoagglutinins in various disease states suggested the extension of the area of investigation. Reported here are (1) primarily leukopenic or neutropenic patients, (2) patients selected irrespective of the presence or absence of leukopenia or neutropenia but with disorders in the categories already reported to have leukoagglutinins, (3) hematologic patients attending our clinic, and (4) patients of all kinds who had had multiple transfusions. As was expected with this approach, new disorders were added to the groups in which leukoagglutinins might be found, and the percentage of nonleukopenic cases rose.

Since it was noted that the earlier investigators had almost invariably found leukoagglutinins in patients who had been given transfusions, special attention was given to persons with multiple transfusions. The transfusions in the development of leukoagglutinins was published by Dausset,[8] who only detailed attempt to assess the role of reported that 90% of his 60 patients with leukoagglutinins had had multiple transfusions. This was corroborated in the present studies; although some of the patients had had very few, nevertheless, 90% of them had had transfusions. It seemed that the multiple transfusions in these patients, noted by all the workers and occurring in almost all the patients, might be the possible common denominator by which the distribution of leukoagglutinins in apparently unrelated diseases might be explained. As is demonstrated in the Figure, the proportion of patients with leukoagglutinins rose as the number of transfusions increased. Transfusion as the common factor in the majority of cases is consistent with the apparent isoactivity rather than autoactivity of the leukoagglutinins in human sera. The development of isoleukoagglutinins during transfusion therapy of four patients in this series and in three of Dausset's[8] is striking

and lends further support to the thesis that leukoagglutinins may be the result of transfusion. Those patients studied by Dausset included two with chronic pancytopenia and one with AHA, all of whom showed a marked and constant leukopenia. Of the four reported here, Patients 249 and 215, both with AHA, and Patient 94, with a pancytopenia, had no leukopenia; Patient 29, with chronic lymphocytic leukemia, had a neutropenia.

If multiple transfusions are proposed as the stimulus for leukoagglutinin formation, then the lack of such formation (Table 5) in many transfused patients requires explanation. In general, immunologic response is determined by the nature of the host, the character of the stimulating antigen, and the frequency of contact with the antigen. It is well known that experimental animals differ in the capacity to produce circulating antibodies to a given antigenic stimulus, and this has been reasonably well established for certain specific antigens in presumably normal healthy persons. Furthermore, in certain disease states, as compared to presumably normal persons, there may be either an exaggerated response or a diminution of response to a given antigenic stimulus. Creger, Choy, and Rantz [29,30] found that 2 of 48 medical students formed excessively large amounts of antibody following stimulation by viral vaccine antigens of influenza A and B, and the same 2 of 48 reacted similarly following the injection of heterologous blood. A similar increase followed in a patient with DLE, in one with erythema nodosum, in one with AHA, and in a small group of rheumatic subjects. Sands et al.,[31] using the same technique of stimulation with mismatched blood, found that patients with sarcoidosis produced significantly higher titers of isoagglutinins than did normal persons. Geller [32] studied the antibody response to Pneumococcus polysaccharide I in normal persons and in patients with malignant lymphomas. He concluded that there was a poverty of antibody response in the lymphoma patients to this antigen, for only 14% to 20% developed good titers; 62% of the controls developed good titers to this antigen.

Related to the occurrence of leukoagglutinins in the leukemic patients with transfusions is the reported greater ability of patients with chronic myelogenous leukemia, antibodies. Larson and Tomlinson [33] demonstrated that patients with untreated acute leukemia exhibited unusually large antibody responses to pneumococcus polysaccharides I and II, while patients wtih chronic lymphocytic leukemia showed little or none. The patients with acute leukemia to produce Hodgkin's disease, and lymphosarcoma in their series showed normal antibody responses. In our results, both patients with chronic and acute leukemia were found to possess leukoagglutinin in their sera.

If further data support the present findings which suggest that isoleukoagglutinins are the consequence of transfusions in persons who are vigorous antibody manufacturers, the role of these antibodies in pyrogenic transfusion reactions must be considered. The multiplicity of factors involved in pyrogenic transfusion reactions makes it difficult to prove that a specific reaction is due to a leukoagglutinin. However, it was felt that the collection of existing references as well as our own experience would be of value in stimulating further investigations on this problem. In the series presented in this paper, there were reports of frequent and violent reactions to the administration of blood in 13 of 32 patients for whom records were available. These reactions were characterized by chills, temperature of 39 C (102.2 F) or over, and occasionally shock. More of the patients with leukoagglutinins may have had reactions, but the variation in style of recording did not permit accurate conclusions. The use of steroids and antihistamines did not appear to moderate reactions in some pationts with leukoagglutinins. Goudsmit and van Loghem,[12] Dausset,[8] and Marchal et al.[9] have all called attention to the occurrence of reactions to transfusions in patients with

leukoagglutinins. It was Dausset's[8] impression that certain shocks after transfusion might have originated from the reaction of leukocytes with leukoagglutinins. He stated that "some of our patients who definitely possess leukoagglutinins show a violent shock after each transfusion, while others, who have leukoagglutinins in the same titre, do not show this reaction."

In terms of the recipient of leukoagglutinins, the recent experimentally induced responses to transfusions of blood containing leukoagglutinins should also be noted. Both a drop in leukocyte count with reaction and a drop in leukocyte numbers without reaction have been described. Moeschlin and Wagner[1] twice administered to normal recipients 300 cc. of blood containing leukoagglutinins drawn from an aminopyrine-sensitive patient three hours after the provoking dose of aminopyrine, when granulocytopenia was most pronounced. The first recipient experienced subjective discomfort and became pale, although no fever or shaking chill appeared. The leukocytes dropped from 5000 per cubic millimeter to 800 in 40 minutes, with recovery after four hours and a doubling of the initial count later; in the second recipient the count fell from 8400 to 1700. Control transfusions of normal blood to these same recipients produced only insignificant variations in the leukocyte count.

Dausset, Nenna, and Brecy[6] reported that in two instances in which transfusion with blood shown to contain a leukoagglutinin was carried out, the recipient developed marked leukopenia. Marchal, Duhamel, Dausset, and Libeskind[9] transfused 150 cc. of compatible serum from a patient with Hodgkin's disease (leukoagglutinin titer 1:32) to another patient with lymphocytic leukemia. Shock was observed clinically; within one-half hour of administration there were facial swelling, dizziness, cyanosis, a drop in blood pressure, and a chill followed by a temperature rise to 39 C. Symptoms disappeared in about an hour. Leukocytes fell from an initial count of 38,000 per cubic millimeter to 5600 in one-half hour, with return to 12,000 in eight hours and to 37,600 the following day. Several days later the administration of 150 cc. of normal serum lowered the leukocyte count from 42,000 to 23,200 without any evidence of clinical shock or other reaction. Miescher[18] performed a similar experiment in which 400 cc. of blood containing leukoagglutinins from a patient with tuberculosis of the spleen was given to a patient with cancer. The ensuing leukopenia lasted over a period of three hours. No mention was made of any other untoward effects. However, in rabbits 3 cc/kilogram of the same serum proved lethal when given intravenously. Normal sera were not lethal at this dosage. Leukocytic emboli were observed in the lungs and kidney of the animal. Absorption with human leukocytes rendered this patient's serum innocuous for rabbits.

There are in the literature, too, reports of transfusions of blood from patients with leukopenia which induced a marked lowering of the peripheral leukocyte count.[34,35] However, leukoagglutinins were not demonstrated in these sera. The transfusion of normal sera by the various investigators did not appear to induce the marked effects either of the sera containing leukoagglutinins or of the sera from leukopenic patients.

From the above material, the possibility may be entertained that some transfusion reactions may be due in part or entirely to the existence of leukoagglutinins either in the recipient or in the donor. The nature of the disease process in which most leukoagglutinins have been demonstrated would ordinarily preclude the use of such persons as donors. From the standpoint of the recipient, the presence of an isoleukoagglutinin in his own serum offers an additional factor to be considered in transfusion reactions.

On the Nature of the Antibody

These studies on the nature of the leukoagglutinin leave the impression that it is

an antibody separate from the factor causing L. E. cell formation, from the factor sensitizing the erythrocyte in AHA and the platelets in ITP, and from the Rh antibody (Table 4), though any one of these antibodies may or may not occur in the same sera in which leukoagglutinins are found. As was shown earlier, absorption of the anti-D component of the serum of Patient 15 did not alter the leukoagglutinin titer. L. E. cells were not observed in patients with leukoagglutinins who did not have DLE. The most frequently encountered leukoagglutinins behaved as panantibodies for all types of leukocytes except those from the same donor. Leukocytes obtained from patients with leukoagglutinins were agglutinable by other agglutinating sera. The results presented here serve as support to the more comprehensive figures provided by Dausset,[8] showing that a high percentage of different donor cells are agglutinated by leukoagglutinating sera. Abnormal protein patterns were not essential for the presence of these agglutinins. The temperature requirements of the leukoagglutinin were like those of immune antibodies and were unlike those of the naturally occurring isoagglutinins for erythrocytes.

An unusual feature of the leukoagglutination reaction was its inhibition by a normally occurring thermolabile serum substance. The inhibiting agent was not capable of reverser activity once agglutination had taken place; thus the action of the inhibitor was different from the agent of normal serum, which reversed the normal agglutinin for trypsin-treated red cells.[36] Nor did the inhibitor act as a blocking antibody of the types seen in the Rh system.

The entire subject of inhibitors of antigen-antibody reactions is an obscure one, and the data relating to inhibitors have not been fully assembled. Before the nature of the thermolabile inhibitor of leukoagglutination is clarified, a number of possibilities explored in other systems will require testing. This inhibitor appears to differ from others in its thermolabile property. A normal serum inhibitor of hemagglutination by virus has been reported as (1) a mucopolysaccharide[37] and (2) a protein.[38] Gerstl et al.[39] reported that cold ethanol fractionation of sera from tuberculous patients made possible the demonstration of antibodies which did not appear to be present in the same whole sera. This is reminiscent of the loss of leukoagglutinin inhibitor by the fractionation of sera using Cohn's techniques. Cann et al.[40] removed an inhibitor in rabbit antisera by fractionation with the electrophoresis convection technique.

Summary

Agglutinins for leukocytes were demonstrated in the sera of 38 of 350 hematologic patients, or in the sera of more than 10% of the persons examined. Fifty presumably healthy medical students were shown not to have agglutinins for leukocytes.

Leukoagglutinins were found in six disease states not previously reported, i. e., refractory anemia in pregnancy, and anemia of liver disease, blood loss anemia associated with esophageal varices and hiatus hernia, myelofibrosis, and neuroblastoma.

Sixty-four per cent of these patients with leukoagglutinins had no leukopenia or neutropenia at the time of testing; sixty-nine per cent were not consistently leukopenic or neutropenic. Examination of the over-all history of these patients showed that 44% had no history of leukopenia or neutropenia.

Thirty-four, or about 90%, of the thirty-eight patients with leukoagglutinins had had transfusions prior to the test. The number of transfusions were as few as 2 and as many as 148. Leukoagglutinins occurred more frequently among subjects who had had many transfusions. There was an increasing trend relating the likelihood of a positive test for leukoagglutinins to the number of transfusions received.

The leukoagglutinins in four patients without a history of transfusion were atypical in character. The leukoagglutinins of three of these patients were not consistently

present several months after the initial tests.

The majority of the leukoagglutinins described behaved as artificially induced isoagglutinins for leukocytes. The possibility that these leukoagglutinins are the result of transfusions in persons who readily manufacture antibodies to antigens of leukocytes was discussed.

Data and discussion were presented on the nature of the leukoagglutinin.

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Comparative Value of Serum and Urinary Amylase in The Diagnosis of Acute Pancreatitis

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The very great importance of a rise in serum amylase concentration for verifying a suspicion of pancreatitis is generally recognized, as is the difficulty that would be encountered in diagnosis without some such measure. Not so widely appreciated is the fact that the serum amylase often fails us, particularly if the episode is mild or the patient is not seen within the first few days. Clearly, any measure of the outpouring of amylase from the pancreas that improves upon the serum concentration should have great practical value.

Though much has been written about urinary amylase, the data and conclusions are conflicting, and in consequence urinary amylase excretion is infrequently used in practice. Since amylase is freely excreted by the kidney it seemed reasonable, on a little reflection, to expect the urinary excretion to give information when the serum concentration could not. This is seen from a consideration of the following hypothetical circumstances. The normal average daily urinary amylase excretion is roughly 2000 units per day, and serum concentration, approximately 100 units per 100 ml. If we assume that but a small fraction of the circulating amylase is metabolized or excreted other than by the kidney, then to maintain the plasma concentration of amylase at 100 units per 100 ml. 2000 units must be entering the circulation each day, presumably largely from the pancreas (Table 1). If the amount of amylase entering the circulation increases to 5000 units per day, the serum concentration would rise to 200 units per 100 ml. if there were no concomitant increase in urinary excretion, and would remain at 100 units per 100 ml. if all of the excess amylase were excreted in the urine. If a larger amount of amylase entered the circulation from the pancreas, say 9500 units, and only 8000 units per day, a frequent level of urinary amylase in mild pancreatitis, was excreted, the entire retention of 1500 units would only raise the serum concentration to 150 units per 100 ml.

TABLE 1.—*Hypothetical Example of Amylase Excretion*

Into Circulation from Pancreas, Units/Day	From Circulation into Urine Units/Day	Net Circulating Concentration* Units/100 Ml.
2,000	2,000	100
5,000	2,000	200
5,000	5,000	100
9,500	8,000	150

*Assuming plasma volume of 3,000 ml.

We do not presume that the assumptions underlying this hypothetical example are strictly correct, nonetheless it illustrates two important facts. Amylase on going from the pancreas into the circulation is diluted and is rapidly excreted by the kidney. Therefore large increments in the amylase released are required to raise the plasma concentration appreciably, and plasma concentration is an insensitive reflector of the total amount of amylase passing through the circulation. Much of the amylase leaving the circulation is concentrated in the

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urine and accumulates there. Therefore the amount excreted in a given time interval might be expected to reflect reasonably well the amount passing through from the pancreas. Wohlgemuth [13] showed long ago that amylase appears in the urine very rapidly after the excretory duct of the pancreas is ligated in the dog. Dankner and Heifetz [1] have shown that amylase appears in the urine very rapidly after the onset of an episode of pancreatitis and that renal function is but transiently and partially compromised in the usual case of pancreatitis.

The prevailing viewpoints concerning the comparative diagnostic value of the urinary amylase are satisfactorily reflected in one of the following three conclusions:

1. The urinary amylase is highly variable and is of little value.[2,3,9]

2. The urinary amylase parallels the serum amylase and is of no additional value.[4,6]

3. The urinary amylase may remain elevated one or two days longer than serum values and may be helpful occasionally.[7,10]

All of these conclusions would be likely to discourage the routine use of urinary amylase excretion in the diagnosis of acute pancreatitis, and in fact its use has been restricted largely to physicians, such as the group at Los Angeles County Hospital,[5,8] whose personal experience has been at variance with these conclusions. One of the main sources of of confusion has been the frequent use of urinary concentration of amylase as a measure rather than the quantitative rate of excretion. The result has been excessive variability introduced by varying urine volumes.

Our own experience leads us to conclude that the urinary amylase excretion is abnormal when the serum amylase is abnormal if renal function is adequate, and it remains abnormal, as a rule, 7-10 days after the serum concentration has returned to normal. We present our evidence in this report.

Methods and Materials

Procedure.—Serum and urinary amylase determinations were by the method of Van Loon, Likins, and Seger.[12] The method involves the incubation of saline-diluted serum or urine with a buffered starch substrate, addition of an iodine solution, and measurement of the intensity of the blue color that forms with polysaccharides.

In the initial phases of the study a 1-hour and a 24-hour urine specimen were analyzed for amylase content. After it became apparent that the 24-hour collection was no better than the 1-hour, we settled on a single two-hour specimen, to ensure an adequate urine volume, and expressed the result in units excreted per hour. Serum and urine specimens were collected within a few hours of each other, when both were obtained. Analyses were completed within one or two days of the collection.

Patients.—Control observations were made on 27 patients from the general medical wards who were convalescing from illnesses in which the pancreas was not involved and who had normal renal function. The diseases represented were hypertension, compensated heart disease, malaria, pharyngitis, otitis media, and various pulmonary diseases, including asthma, emphysema, and lung abscess. None of these patients had a previous history suggesting acute or chronic pancreatitis. Serum, 1-hour urine, and 24-hour urine specimens were collected for analysis on each of two consecutive days.

Serial observations were made during 21 episodes of acute pancreatitis occurring in 19 patients without evidence of renal dysfunction. Similar observations were made in two patients with known renal disease, one of whom had clear-cut episodes of recurrent pancreatitis. In addition one patient with salivary gland inflammation was studied briefly. These patients were consecutive admissions. No instance of acute pancreatitis that we knew about was omitted.

Stability of Amylase.—Stability of amylase in serum or urine was tested for by allowing specimens to stand at room or refrigeration temperatures for as long as one week before repeating the analysis. The replicate values are given in Table 2. The variations observed were no greater than the variations between duplicates analyzed simultaneously. Stocks [11] had observed a similar stability.

Technical Variations.—In 12 control patients one-hour urine specimens were analyzed in duplicate. The differences between the two determinations were random as shown in Table 3, the average difference being nearly zero. The average absolute difference, i.e., without regard to sign, was 14% of the mean of the two values recorded per patient.

Diurnal Variations.—In 23 control patients two-hour urine collections were made on arising in the morning and before bedtime at night. The

TABLE 2.—*Stability of Amylase in Urine and Serum* *

Sample	Initial Value	Repeat Values, Days					Comment
		1	2	3	4	6-8	
Urine							
1	149	...	...	...	144		Refrig.
2	131	134	129				Rm. temp.
3	78	88	82				Rm. temp.
4	185	196	195				Rm. temp.
5	331	...	323	...	350		Rm. temp.
6	3,860	...	...	4,610			Rm. temp.
7	347	320	...	...	327		Rm. temp.
8	457	423	...	...	439		Rm. temp.
9	362	336	...	344			Rm. temp.
10	10,102	...	...	...	...	9,350	Rm. temp.
11	676	...	...	...	...	644	Rm. temp.
12	380	...	...	...	...	374	Rm. temp.
Serum							
1	405	394	...	408			Rm. temp.
2	301	324					Rm. temp.
3	131	...	...	...	140		Rm. temp.
4	794	...	...	...	...	807	Frozen

* All values are concentrations in units/100 ml.

differences in amylase excretion were random as shown in Table 3. The average absolute difference was 29%. Of course this cannot be generalized to the sleeping hours at night.

Day-to-day variation in one hour urine amylase excretion is also shown in Table 3. The average absolute difference for two consecutive days was 35%. This is to be contrasted with the corresponding value of 22% for serum concentration and of 19% for 24-hour urine excretion as summarized in Table 4.

Normal Values.—Serum, 1-hour urine and 24-hour urine amylase values obtained in the 27 patients without pancreatic disease are summarized in Table 5. The highest single serum amylase concentration observed in any one person on either day of the determination was 191 units per 100 ml.; the highest single one-hour urine excretion was 264 units per hour; the highest single 24-hour urine excretion was 4264 units per day. In order to maintain comparability among the measures for purposes of the present analysis, we therefore took as approximate limits of normal for serum amylase concentration 200 units per 100 ml.; for 1-hour urine amylase excretion, 280 units per hour, and for 24-hour urine amylase excretion, 4000 units per day. For general clinical application 300 units per hour may be taken as a convenient and reasonably accurate limit of normal for urinary amylase excretion.

Analysis.—The serum and urine amylase data are charted serially for each patient in Figures 1-7. The ordinate of the graphs is so constructed that the range of normal of each measure is subdivided into four class intervals. The measures are thus approximately comparable in terms of

TABLE 3.—*Technical and Diurnal Variations in One-Hour Urine Amylase Excretion* *

Determination		Time of Day		Day to Day	
Original	Repeat	A.M.	P.M.	First	Second
82	103	82	79	59	49
61	82	61	88	117	88
173	164	173	169	156	81
65	54	65	100	108	88
183	171	183	245	137	78
229	213	229	174	116	51
42	52	42	75	39	36
264	246	76	112	180	125
74	56	91	85	63	53
93	84	69	147	147	233
60	57	165	178	134	117
159	149	137	246	130	244
		112	77	129	127
		140	93	83	214
		92	80	92	125
		59	79	179	158
		116	155	76	88
		162	104	103	224
		125	127	109	125
		66	64	66	56
		117	127	44	93
		57	108	87	91
		103	82	264	137
				226	188
Percentage Difference†					
Mean	14%	29%		35%	
Range	5%-29%	2%-72%		2%-88%	

* All values are units per hour.
† Absolute difference as a percentage of the mean of the two values recorded per patient.

TABLE 4.—*Day-to-Day Variation of Amylase Values in the Normal Range*

	No. of Cases	Absolute Differences			
		Actual		Percentage*	
		Mean	Range	Mean	Range
Serum, units/100 ml.	26	20	1-104	22	1-81
1-hr. urine, units/hr.	24	46	2-131	35	2-88
24-hr. urine, units/day	26	338	1-1,255	19	0-68

* Absolute difference as a percentage of the mean of the two values recorded per patient.

class intervals. The limit of normal is indicated by the light horizontal line drawn across the graphs at the level of the fourth class interval. The abscissa records the interval in days following admission during which the laboratory studies were made. For each variable the available points are connected consecutively to bring out the sequence of changes. However, values were not always available for every variable on any given day, so comparisons of the curves will occasionally be misleading unless the plotted points are specifically taken into account. Values exceeding 750 units/100 ml. for serum concentration, 1050 units per hour for 1- or 2-hour urine excretion, and 15,000 units per day for 24-hour urine excretion are recorded vertically at the top of each graph opposite the appropriate day of the observation.

Results and Interpretations

Time Sequence.—Figures 1-7 present the amylase data serially for each patient during the period that urine collections were made. The first seven patients in Figures 1 and 2 and the two patients with renal insufficiency, Case 21 (Fig. 7) and Case 22, had 24-hour as well as 1-hour collections. It was apparent from a comparison of the 1-hour and 24-hour excretions in these nine patients that the larger collection period had no special advantages. In 22 of 29 simultaneous observations made in these nine patients, the 1-hour and 24-hour values were both normal or abnormal to approximately the same degree. In six the 1-hour excretion was relatively more abnormal, and in one instance the 24-hour excretion was significantly more abnormal. The parallelism of 1-hour and 24-hour urine amylase under irregular conditions of excretion is particularly well shown in a patient with extrarenal uremia whose data are portrayed in Figure 7. In view of these observations as well as its inherent disadvantages the 24-hour collection period was discontinued.

The following summaries present the essential clinical data of each patient.

CASE 1.—A 35-year-old jaundiced man who had had intermittent attacks of abdominal pain in the right upper quadrant for many years was hospitalized two days after a recurrent episode of pain which radiated through to his back and was associated with nausea, vomiting, and dark urine. His pain subsided promptly, though his icterus persisted, and he was ambulated on the fourth day. On the seventh day he had recurrent pain, at which time his serum amylase became abnormal and urine studies were requested (Fig. 1). The pain again subsided rapidly only to recur severely on the 12th day, one day after a gastrointestinal series was performed. At exploration the following day the head of the pancreas was edematous and enlarged, the common bile duct (CBD) was slightly dilated, and one stone was found in the gallbladder, which was removed. There was no fat necrosis. He improved clinically following surgery, and the tube was removed, and oral feedings were begun on the 16th day. Though he showed a rise in amylase excretion on the 19th and 21st days, he was discharged with an indwelling

TABLE 5.—*Amylase Values in Twenty-Seven Patients Without Pancreatic Disease*

	Mean*	Range, %*		Lowest Single Value	Highest Single Value
		10-90	0-100		
Serum, units/100 ml.	90	62-117	44-139	38	191
1-hr. urine, units/hr.	118	61-187	38-207	36	264
24-hr. urine, units/day	1,947	940-3,123	852-4,224	792	4,264

* Average of 2 consecutive days' determinations utilized in these calculations.

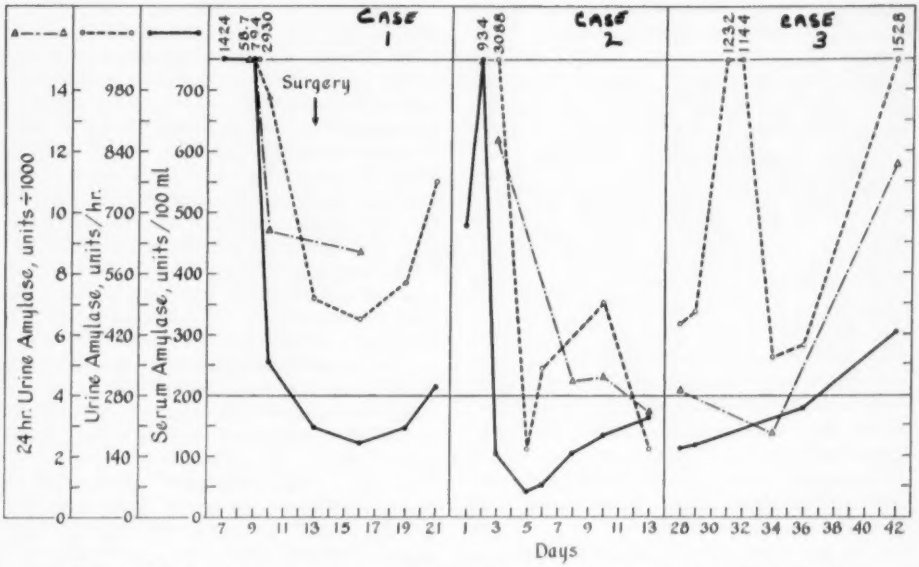

Fig. 1.—Serial serum and urine amylase values of Cases 1, 2, and 3. Determinations falling above the limits of each graph in this and subsequent figures are recorded vertically at the top of the graph in line with the day of the observation and plotted on the demarcation line drawn at the level of the 15th class interval. For each variable the available points are connected consecutively to bring out the sequence of changes. However, values were not always available for every variable on any given day, so comparisons of the curves will occasionally be misleading unless the plotted points are specifically taken into account. For example, Case 3 has no serum values corresponding to the third and fourth one-hour urine values, so the curves cannot be compared in this region.

T-tube in his CBD. This was removed after two months during which he was essentially asymptomatic.

Case 2.—A 59-year-old man was hospitalized one day after the onset of severe upper abdominal pain. He was febrile and mildly jaundiced. He was aware of having pernicious anemia in remission and previously asymptomatic cholelithiasis. Within 4 days he was eating, and by the 10th day he seemed well. His serum amylase plunged to normal levels by the third day, however, his urinary excretion rate was still abnormal on the 10th day (Fig. 1). Gallstones were demonstrated by a cholecystogram. A gastrointestinal series was normal. One month later he was subjected to cholecystectomy and CBD drainage.

Case 3.—A 35-year-old man with a Billroth I gastrectomy had his stomach reresected on the 14th day of hospitalization for a recurrent posterior penetrating gastric ulcer which was adherent to the pancreas. He developed a subhepatic abscess, which was opened on the 20th day, after which a pancreatic fistula drained 1.0-1.5 liters of fluid a day for a prolonged period. From the 25th to 50th days he had many attacks of abdominal pain associated with fever, nausea, retching, and distention. The chart (Fig. 1) records serum and urine observations made between the 28th and 42d days. The amylase concentration of the fistula fluid was 16,300 units/100 ml. on the 28th day. He eventually recovered five months later, requiring two further explorations and radiation therapy before the inflammation subsided and the fistula closed.

Case 4.—A 40-year-old Negro slaughter-house worker complained of shaking chills and fever, headache, stiff neck, muscular aching, abdominal pain, nausea, vomiting, and diarrhea. He was tender in the right upper quadrant and epigastrium anteriorly and in the costovertebral angles bilaterally posteriorly. His white blood cell count and sedimentation rate were elevated. His hemoglobin concentration was 9.2 gm/100 ml. on admission and rose slowly to 14.0 gm/100 ml. over the next 13 weeks. ECG was consistent with pericarditis. His serum bilirubin was 1.6 mg/100 ml., and sulfobromophthalein (Bromsulphalein) retention, 10% in 45 minutes. A fasting blood sugar was slightly abnormal. Blood, urine, and spinal fluid cultures were negative. Agglutination tests were positive for Leptospira pomona. Amylase studies (Fig. 2) were performed because of the abdominal pain. He was treated with tetracycline and improved rapidly. The final clinical

diagnosis was leptospirosis with meningeal, cardiac, hepatic, pancreatic, and renal involvement.

Seven months later he was readmitted with symptoms suggesting diabetes mellitus. A fasting blood sugar and glucose tolerance test were abnormal. There was no family history of diabetes.

CASE 5.—A 42-year-old man complained of intermittent upper abdominal pain and vomiting for many months. He was slightly febrile, and a small mass was palpable in the left upper quadrant of his abdomen. Two years previously he had had a cholecystectomy, sphincterotomy, and drainage of a pseudocyst in the head of the pancreas. One year previously he had been readmitted with a mild recurrence of acute pancreatitis.

He appeared to do well until the seventh day, when he had a chill and fever following a barium-enema study and lapsed into shock. His hemoglobin concentration dropped rapidly from 14.4 to 11.7 gm/100 ml. without external evidence of bleeding. A blood culture was negative. The serum bilirubin concentration rose to 2.1 mg/100 ml. He improved gradually, however, fever, pain, and the mass persisted, and he was explored on the 17th day, at which time urine studies were begun (Fig. 2). A pseudocyst of the tail of the pancreas containing approximately 1 liter of bloody fluid was resected. He recovered rapidly and was asymptomatic on follow-up examination three months later.

CASE 6.—A 42-year-old former alcoholic was admitted for CBD transplantation because of repeated attacks of acute pancreatitis. Fifteen months previously he had been explored for a perforated duodenal ulcer and was found to have pancreatitis. Five months later he had a cholecystectomy and sphincterotomy which did not relieve the attacks entirely. Glucose tolerance was abnormal. Amylase values are given in Figure 2. He was asymptomatic, and choledochoduodenostomy was carried out uneventfully.

He was readmitted one year later with recurring upper abdominal pain precipitated three months previously by an automobile accident in which he suffered a blow to his abdomen. Serum amylase at another hospital four days before admission was 3000 units/100 ml. Our studies are shown in Figure 3. His pain, fever, and leukocytosis subsided in seven days, as did his urinary amylase, and he was discharged on the eighth day despite a rebound of his urinary amylase. At our request a white cell count was obtained before he left the hospital. It was 20,000 cells/cubic millimeter.

CASE 7.—A 58-year-old alcoholic complained of crampy upper abdominal pain and vomiting. He had had many such attacks. He manifested a slight fever, abdominal tenderness, ileus, elevated sedimentation rate, and slightly abnormal fasting blood sugar. A midday urinary amylase determination was abnormal, even though the total 24-hour

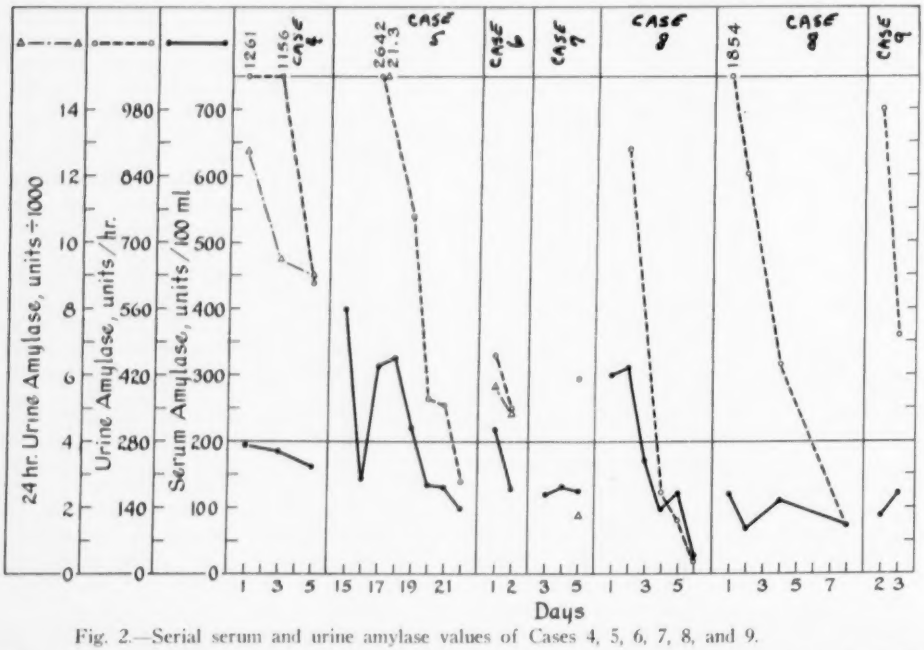

Fig. 2.—Serial serum and urine amylase values of Cases 4, 5, 6, 7, 8, and 9.

excretion fell within the normal range (Fig. 2). He left the hospital against advice on the seventh day with a presumptive diagnosis of acute recurrent pancreatitis.

CASE 8.—A 30-year-old Negro serviceman complained of upper midabdominal pain unrelieved by vomiting. He had had five similar previous attacks, each diagnosed acute pancreatitis. He recovered rapidly (Fig. 2) and was transferred to a Navy hospital on the sixth day.

Six months later he was readmitted with similar complaints and epigastric tenderness. Serum amylase values were normal, and urinary excretion, abnormal (Fig. 2). He improved rapidly, however, recovery was delayed by his development of a toxic psychosis due to alcoholism.

CASE 9.—A 30-year-old man complained of malaise, muscular aches, chilliness, fever, and sore throat. He had enlarged tender submaxillary glands, cervical adenopathy, and pharyngitis. His temperature was 103 F, and white blood cell count, 26,400/cubic millimeter. Beta-hemolytic streptococcus was cultured from his throat. His sialadenitis resulted in abnormal urinary excretion of amylase (Fig. 2). He responded promptly to penicillin.

CASE 10.—A 47-year-old alcoholic had pain in the upper abdomen, nausea, and vomiting for one week before admission. He had had similar pain previously and had been hospitalized once with a diagnosis of acute pancreatitis. After admission his pain and fever persisted for six days, after which gastric suction was discontinued and oral feedings started. A mild recurrence followed and his urinary amylase rose transiently as shown in Figure 3. A second transient recurrence of nausea and pain occurred on the 14th day following a gastrointestinal series and cholecystogram, which were normal. He was discharged on the 18th day, being asymptomatic and having normal serum amylase. The same day his urine amylase was slightly abnormal; his white cell count, 11,550/cubic millimeter, and his sedimentation rate, 52 mm. in one hour.

CASE 11.—A 40 year-old bibulous bartender complained of upper abdominal pain with radiation to the left shoulder and vomiting for three days. He was febrile and had upper abdominal tenderness. A white cell count was 22,000/cubic millimeter. He improved rapidly and was started on oral feedings on the fourth day, at which time his white count was 11,450/cubic millimeter. Stools were negative for occult blood, and a gastrointestinal series on the fifth day was normal. He was afebrile by the 7th day, however, his urinary amylase was rising (Fig. 3), and on the 10th day his white cell count was 20,350/cubic millimeter, and sedimentation rate, 96 mm. in an hour. He remained symptom-free and was discharged on the 14th day with a diagnosis of alcoholic gastritis, which we would replace with acute pancreatitis.

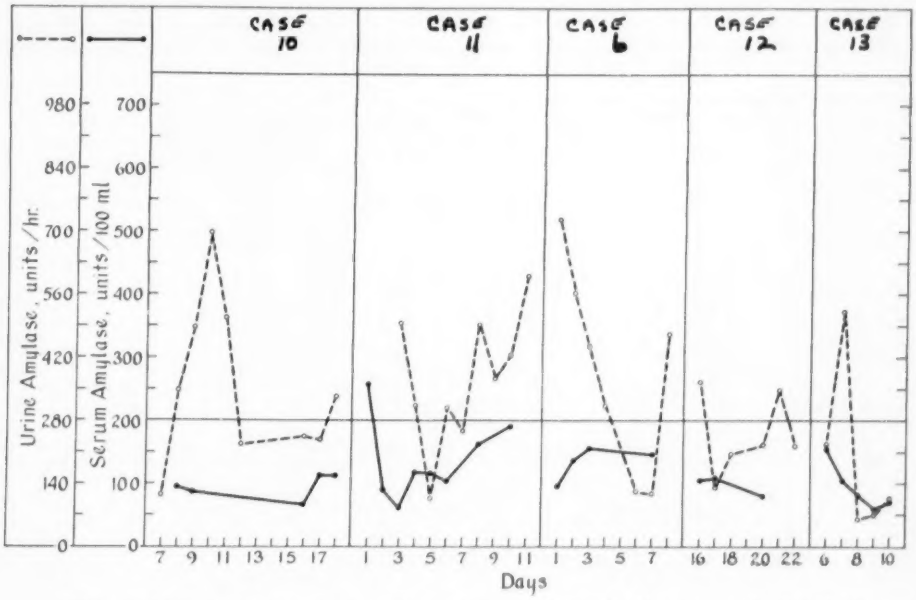

Fig. 3.—Serial serum and urine amylase values of Cases 10, 11, 6 (second admission), 12, and 13.

CASE 12.—A 64-year-old jaundiced man complained of pain in the right upper quadrant, nausea, and vomiting. He was explored for cholecystitis and choledocholithiasis. No gallstones were found, however, his gallbladder was inflamed and tense and his CBD was dilated and thickened. Minimal fat necrosis was evident about the pancreas, which appeared slightly inflamed. Three days after surgery the patient developed a transient acute toxic psychosis lasting but three days. The first urine amylase value obtained one week following surgery was slightly abnormal (Fig. 3). Otherwise his convalescence was rapid and uneventful.

CASE 13.—A 67-year-old man complained of fever, abdominal pain, nausea, and vomiting for several days. Two years previously a pseudocyst in the tail of his pancreas was resected, and nine months previously a CBD transplant was performed because of recurrent symptoms and the presence of a mass in the head of the pancreas. He was treated for acute pancreatitis and improved rapidly, being asymptomatic by the fifth day. On the seventh day his urine amylase was transiently abnormal (Fig. 3), and the next day he was slightly febrile. Recovery otherwise was uneventful.

CASE 14.—A 43-year-old alcoholic complained of recurrent upper abdominal pain, fatty food intolerance, and diarrhea for two years. Three weeks previously, following excessive drinking, he suffered abdominal pain, hematemesis, and melena. In addition to antacids he received chlorpromazine, 25 mg. t. i. d., which he took until admission. Three days previously nausea and vomiting recurred and he became jaundiced. His jaundice was obstructive in type, and a diagnosis of chlorpromazine toxicity was entertained. Because of his complaint on the fourth day of "gas pains" in his upper abdomen following a gastrointestinal series, amylase studies were performed, with the results seen in Figure 4. By the 15th day he had no complaints, and recovery from his toxic hepatitis was complete by the 23d day.

Pancreatitis was not suspected clinically in this man. He was studied because we were looking for patients with abdominal pain. To rule out a possible effect of chlorpromazine, three asymptomatic psychiatric patients receiving moderate or large doses of chlorpromazine were studied. All had normal serum and urinary amylase values.

CASE 15.—A 31-year-old alcoholic complained of upper abdominal pain, nausea, vomiting, and fever for five days. He was febrile and manifested abdominal tenderness. His white cell count was 20,000/cubic millimeter, and his sedimentation rate, 80 mm. in one hour. A clinical diagnosis of acute pancreatitis was made despite a normal serum amylase, and urinary studies were started (Fig. 4). Liver function tests were abnormal but improved rapidly. Gastric suction was discontinued on the third day and a cholecystogram and gastrointestinal series performed. This was followed by a transient rise in urinary amylase for two days. By the seventh day his temperature was normal, however, the white cell count was 20,900/cubic millimeter, and the sedimentation rate, 67 mm. in an hour. His abdomen was still tender, and he noted moderately severe pain on deep palpation in the left upper quadrant. His left diaphragm was elevated on x-ray. A repeat cholecystogram

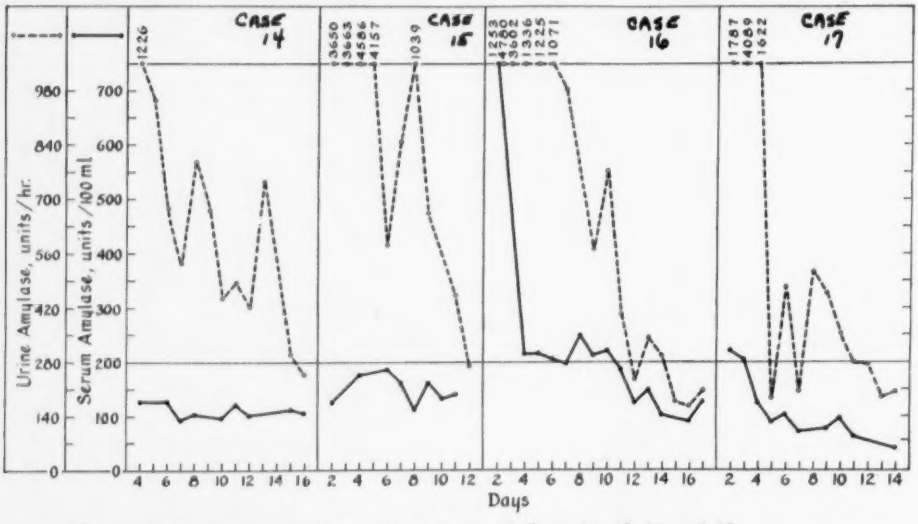

Fig. 4.—Serial serum and urine amylase values of Cases 14, 15, 16, and 17.

and a barium enema performed on the seventh and eighth days, respectively, were followed by a transient rise in urinary amylase. By the 14th day he was essentially asymptomatic, though there was still a vague resistance in the upper left abdomen. The gastrointestinal series, barium enema, and second cholecystogram were normal.

In this patient, the clinical diagnosis, hospital course, and laboratory findings were corroborated by the urinary amylase excretion but not by the serum amylase concentration.

CASE 16.—A 30-year-old bibulous bartender complained of upper abdominal pain for five days. His abdomen was tender, he was febrile, his white cell count was 15,000/cubic millimeter, and he had a trace of sugar in his urine as well as a fasting blood sugar of 142 mg/100 ml. Four years previously an exploration for "appendicitis" revealed acute pancreatitis. Subsequently, after recurrent bouts of abdominal pain, he had a cholecystectomy and sphincterotomy. Following admission his temperature gradually fell to normal by the eighth day, and his abdominal tenderness relented slowly. His serum amylase dropped precipitously, while his urinary excretion more or less paralleled the clinical course (Fig. 4). On the 16th day his white cell count was 10,500/cubic millimeter, and his sedimentation rate, 28 mm. in one hour. He was discharged the next day.

CASE 17.—A 33-year-old alcoholic complained of acute upper abdominal pain, nausea, and vomiting for one day. He was markedly tender in the epigastrium. He was slightly febrile, and his white cell count was 24,400/cubic millimeter. He had had two other episodes of pancreatitis seven and eight years previously. His urinary amylase was markedly abnormal, while his serum concentration was but slightly abnormal (Fig. 4). The abdominal tenderness receded gradually, as did his fever. By the 11th day he only noted slight epigastric tenderness and tolerated a low fat diet. Thereafter his improvement was continuous. Gastrointestinal series and cholecystogram were normal on the 22d day.

CASE 18.—A 55-year-old former alcoholic complained of generalized abdominal pain for one day. The pain localized to his epigastrium, where rebound tenderness was elicited. His temperature varied between 99 and 102 F, and his white cell count was 16,800/cubic millimeter. He had had several previous episodes of severe upper abdominal pain. For the first 14 days there was little change in the abdominal pain, localized tenderness, fever, and leukocytosis, after which improvement was rapid. On the 16th day gastric suction was stopped. Mild pain and tenderness persisted for three more days, after which he became asymptomatic. The relatively greater abnormality of urinary as compared to serum amylase during the symptomatic period is shown in Figure 5. One month after convalescence cholecystectomy and choledochoduodenostomy were performed. Some evidences of fat necrosis were present at surgery. The gallbladder and CBD were normal.

CASE 19.—A 59-year-old bartender complained of acute upper abdominal pain for six days. He

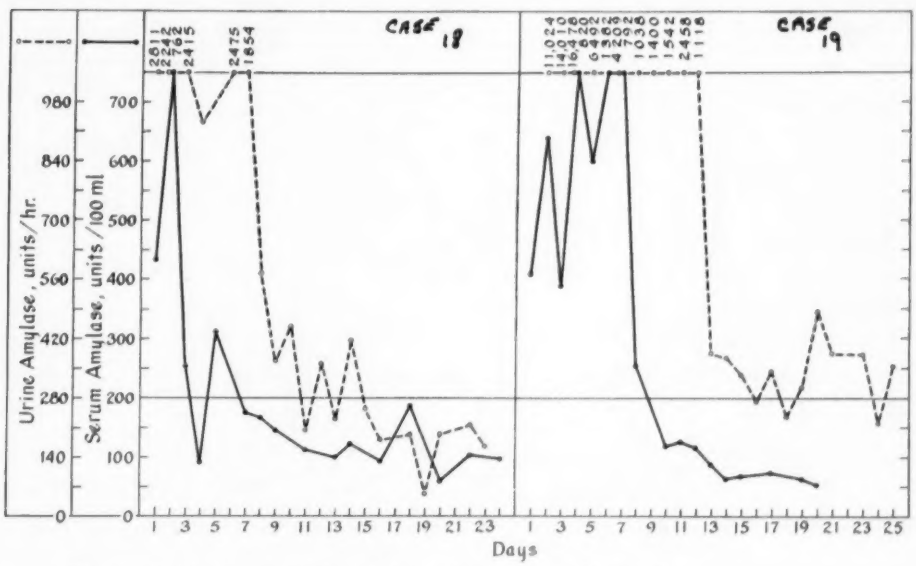

Fig. 5.—Serial serum and urine amylase values of Cases 18 and 19.

admitted to only one previous episode of abdominal pain. He was hospitalized two years previously for acute alcoholism with delerium tremens. On admission his temperature was 104 F; his white cell count, 20,000/cubic millimeter, and his serum bilirubin, 2.3 mg/100 ml. He required gastric suction, parenteral fluids, antibiotics, antispasmodics, and narcotics for 16 days before improvement was evident. His temperature was not normal until the 20th day, at which time he still had a mild leukocytosis. His urinary amylase was abnormal 15 days after his serum concentration had become normal and was always relatively more abnormal during the entire course of the illness (Fig. 5). A gastrointestinal series and cholecystogram were normal on the 21st day. Convalescence was rapid thereafter, except for transient mild fever on the 23d and 24th days, and he was discharged on the 32d day.

CASE 20.—A 38-year-old man complained of pain in the left upper quadrant, nausea, and vomiting of 12 hours' duration. He had been jaundiced following a similar attack six years previously, at which time he was thought to have gallstones. He had gotten along reasonably well since then on a low fat diet, although he had numerous mild attacks of pain. Examination revealed an obese man who was acutely ill, with a temperature of 103 F. His upper abdomen was board-like and generally tender, and his bowel sounds were hypoactive. Two plus albuminuria and bilirubinuria were present on urinalysis. Blood hemoglobin was 18.8 gm/100 ml.; WBC, 28,000/cubic millimeter, with 93% neutrophiles. Serum electrolytes were normal, as were all liver function tests except the bilirubin concentration, which was 1.9 mg/100 ml. Flat and upright films of the abdomen revealed adynamic ileus without free gas. Serum and urinary amylase were abnormal, as charted (Fig. 6). Within two days of admission a definite mass became evident in the left upper quadrant.

He was treated with gastric suction, antibiotics, antispasmodics, sedatives, and narcotics as needed, in addition to parenteral fluids, electrolytes, and blood. This was continued for 20 days, during which time he lost 25 lb. and had varying abdominal pain, prominence of the mass, fever, and leukocytosis. The serum amylase was normal by the fourth day, however, the urinary amylase fluctuated in the abnormal range, decreasing gradually. After the 20th day the mass was no longer palpable, abdominal tenderness was minimal, and he was almost afebrile. His blood hemoglobin was 14.4 gm/100 ml., and his blood sugar and serum electrolytes were normal. The gastric tube was removed and oral feeding started. Treatment was otherwise continued as before, and a low fat diet was tolerated for the next nine

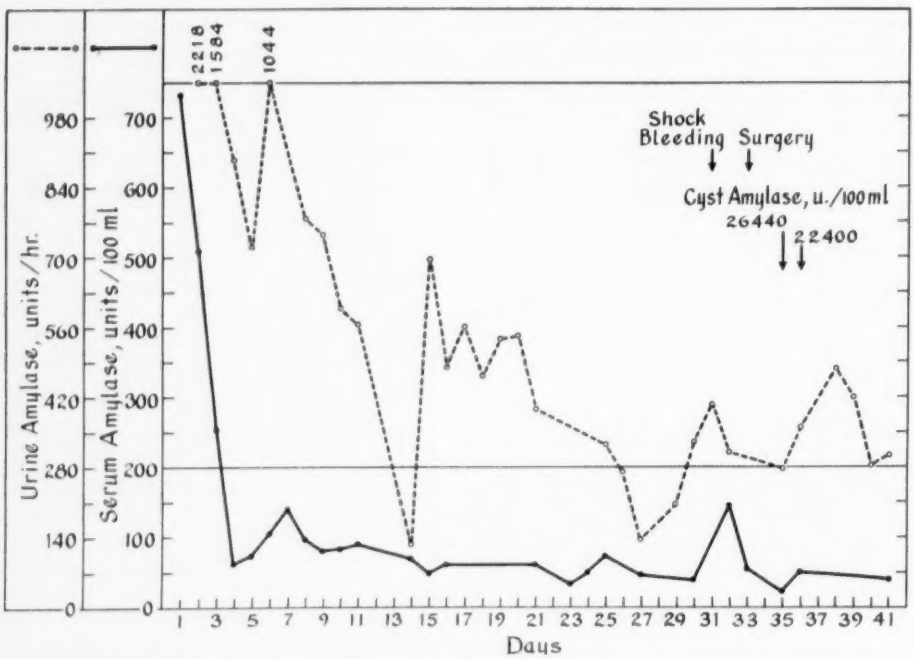

Fig. 6.—Serial serum and urine amylase values of Case 20.

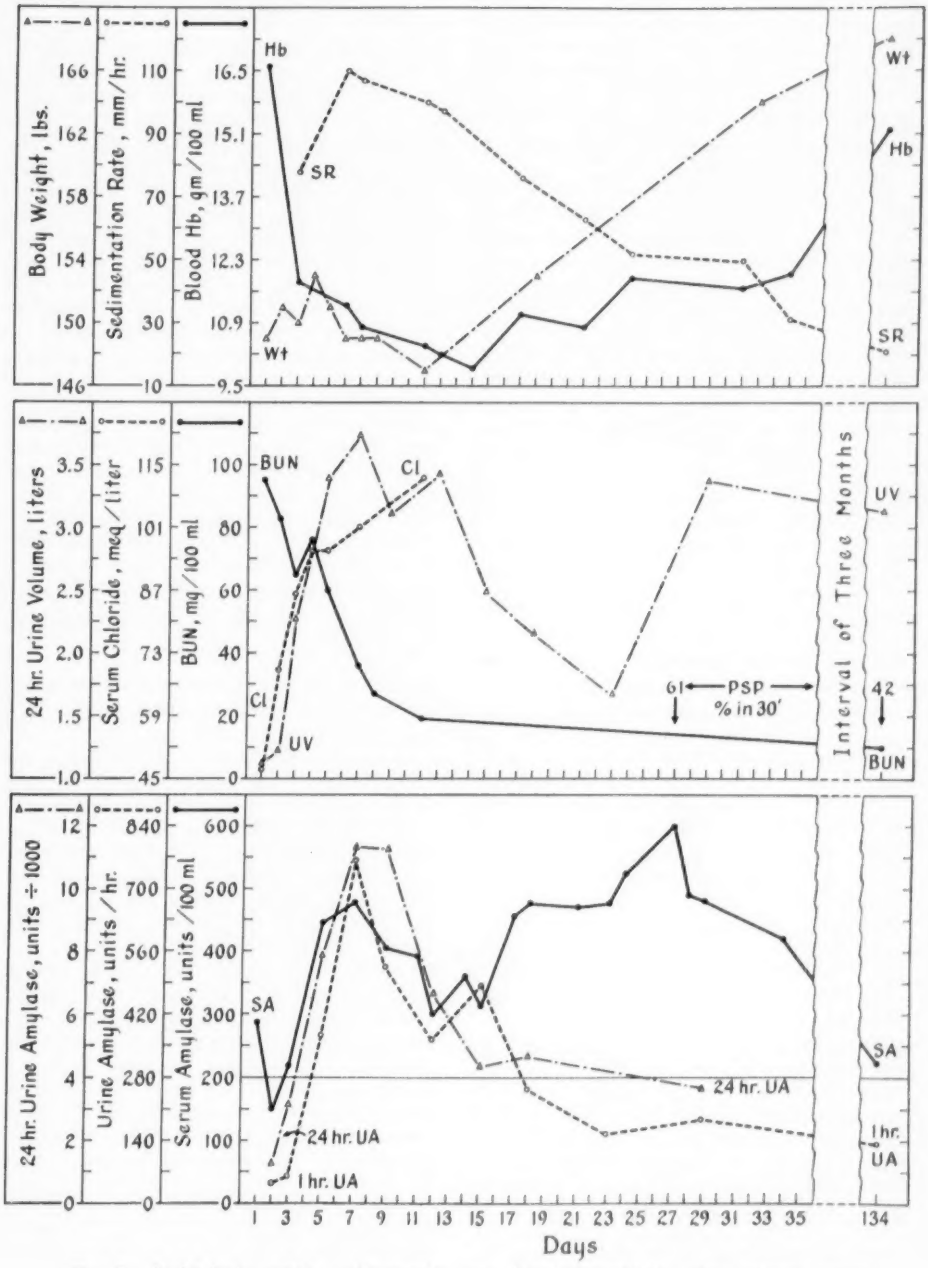

Fig. 7.—Serial body weight, sedimentation rate, blood hemoglobin, urine volume, serum chloride, blood urea nitrogen, and serum and urine amylase values of Case 21.

days, during which time his WBC fluctuated about 14,000/cubic millimeter and his temperature about 99 F. His urinary amylase dropped into the normal range on the 26th day. On the 27th day a cholecystogram was abnormal showing no concentration of dye, and a gastrointestinal series delineated clearly an extrinsic mass, presumably a large pancreatic cyst. In view of what followed the manipulations involved in these procedures were clearly unfortunate.

The patient seemed to do well for the next three days, although some tenderness on palpation was noted in the upper abdomen, and his urinary amylase became abnormal again. The next day—the 31st day—he suddenly began to vomit bright red blood and lapsed into shock, his hemoglobin dropping to 10.1 gm/100 ml. He was given 4500 ml. of whole blood over two days and then explored when bleeding persisted. He was found to have a large pseudocyst of the pancreas, containing approximately 1800 ml. of fluid. The cyst was intimately adherent to surrounding structures, including the stomach, and bleeding from an antral gastritis, and a superficial duodenal ulcer was noted. The gallbladder and common duct were normal. Catheter drainage of the cyst, vagotomy, and pyloroplasty were performed. The amylase concentration of the cyst fluid was 26,440 and 22,400 units per 100 ml. on two occasions. The urinary values continued slightly abnormal over the next eight days, when collections were stopped.

Postoperatively the patient did well, and on the fourth day the gastric tube was removed, an ulcer diet with skimmed milk being well tolerated. By the 15th postoperative day pancreatic drainage was only 50 ml., and his temperature and abdominal findings were normal. He was observed in the hospital until the pancreatic catheter was removed, two months after the operation. At that time a cholecystogram and gastrointestinal series were normal.

In summary, continued activity in a patient with prolonged pancreatitis and a pancreatic pseudocyst was reflected in the quantity of amylase excreted in the urine but not in the serum concentration.

Case 21.—A 45-year-old Mexican, who had been drinking excessively for three weeks, complained of upper abdominal pain, nausea, and severe vomiting for one week. He was markedly dehydrated generally and moderately tender in the epigastrium and right upper quadrant. His initial white blood cell count was 19,700/cubic millimeter; sedimentation rate, 78 mm. in one hour; hemoglobin concentration, 16.6 gm/100 ml.; BUN, 95 mg/100 ml.; chlorides, 47 mEq/liter, and CO_2, 26.6 mEq/liter. The sequential changes in his body weight, sedimentation rate, blood hemoglobin concentration, urine volume, serum chlorides, BUN, serum amylase, 1-hour urine amylase, and 24-hour urine amylase over a 36-day period of hospitalization are presented graphically in Figure 7.

He was treated for acute pancreatitis and extrarenal uremia. Within three days his dehydration was markedly improved and his abdominal pain had subsided. A low-grade fever persisted for two weeks. With the forcing of fluids during the first three days his azotemia cleared rapidly and his urine output reached a peak on the seventh day, as did his urinary amylase. However, parenteral fluids were discontinued, and his daily intake of fluids dropped from 4 liters to 1 to 2 liters, resulting in a corresponding decrease in urine volume and in amylase excretion. During the last three weeks of hospitalization his renal function continued to improve, however, his clearance of amylase remained low. On the 27th day his PSP excretion rebounded to 61% in 30 minutes, probably reflecting the hyperfunction of a mildly damaged organ. His sedimentation rate dropped gradually to almost normal limits by the 34th day, and he gained 15 lb. in weight. Three months later his blood hemoglobin was 15.2 gm/100 ml.; sedimentation rate, 21 mm. in one hour; BUN, 10 mg/100 ml.; PSP excretion, 42% in one-half hour; creatinine clearance, 109 ml/minute; serum amylase, 223 units/100 ml., and urine amylase, 133 units/hour.

Before discharge hepatic function tests were normal, as were a cholecystogram, a gastrointestinal series, a barium enema, and an intravenous pyelogram.

Six months after the episode described he was readmitted under similar circumstances and with similar, though less severe, abnormalities. His hemoglobin was 17.8 gm/100 ml.; BUN, 69 mg/100 ml.; chlorides, 69 mEq/liter, and serum amylase, 440 units/100 ml. Within one week all the measures had reverted to normal, with the possible exception of the serum amylase, which dropped to 198 units/100 ml.

Case 22.—A 41-year-old asymptomatic man was hospitalized because of an elevated serum amylase obtained in a follow-up clinic. Twenty years previously he had been treated for acute glomerulonephritis. Two years previously he had a cholecystectomy and CBD exploration for severe acute cholecystitis and cholelithiasis. His serum amylase ranged from 420 to 708 units/100 ml. preoperatively and rose transiently to 1209 units/100 ml. postoperatively. His pancreas was moderately enlarged and inflamed at surgery. Prior to discharge four months later his PSP excretion was only 15% in one-half hour. His BUN was normal. He was observed for six months while a T-tube was in his CBD. At all times his serum amylase remained about 300-400 units/100 ml.,

TABLE 6.—*Amylase Values in Case 22*

Day	Serum, Units/100 Ml.	1-Hr. Urine, Units/Hr.	24-Hr. Urine, Units/Day
3	330	372	1,932
5	319	156	2,238
8	310	67	2,210
14	306	140	2,376

the level observed at this admission. On the 3d, 5th, 8th, and 14th days of hospitalization he was observed to have serum and urine amylase values as shown in Table 6. The serum values were presumably related to his chronic subclinical renal insufficiency primarily.

Frequency of Abnormal Values.—Two of the 19 patients with acute pancreatitis uncomplicated by renal insufficiency were observed twice, providing 21 periods of hospitalization for analysis. In each of these 21 patient studies (as well as that of the patient with sialitis) the urinary amylase excretion was abnormal one or more times when the serum concentration was normal. All told, the urinary amylase excretion was abnormal 83 times (including two measurements in the patient with sialitis) when the serum concentration was normal. The serum concentration was never abnormal when the urine excretion was normal. In every instance where both were abnormal, the relative degree of abnormality of the urinary excretion exceeded that of the serum concentration. Though marked variations depending upon the nature of the episode were to be expected, the serum concentration usually returned to normal within 4 days, and the urinary excretion generally remained abnormal 7 to 10 days longer. In the instance of Case 20, with a large cyst as a continuing source of amylase, the urinary excretion remained abnormal at least 37 days after the serum concentration had returned to normal.

In none of the foregoing patients was renal dysfunction a problem. BUN's on admission varied from 5 to 29 mg/100 ml. Those values over 20 mg/100 ml. promptly dropped to the range of 10-15 mg/100 ml. within one or two days. When significant renal insufficiency complicates an episode of acute pancreatitis transiently, as in Case 21, or exists chronically, as in Case 22, neither the serum nor the urinary amylase gives reliable information.

Comment

The relative superiority of the urinary amylase excretion over the serum amylase concentration is unequivocal in the patients we have studied. In no instance was the serum concentration abnormal when the urine excretion was normal except in the presence of renal insufficiency, in which case neither measure is valid. We are led to recommend the use of the urinary amylase routinely in preference to the serum determination if only one procedure is to be used. Wide variations are to be expected in the extent to which the urinary excretion lags behind the serum concentration in their return to normal levels, depending upon the severity of the episode and the reservoir of unexcreted amylase. In mild episodes which pass over promptly, such as the first admission of Case 8, in Figure 2, the urinary values may plunge to normal almost as rapidly as the serum levels. At the other extreme patients with severe pancreatitis and pseudocyst formation may have a continuing source of amylase feeding slowly into the circulation for many weeks, resulting in prolonged periods of abnormality of urinary excretion only, as in Case 20, in Figure 6. The typical patient sent to a reference hospital such as ours has his illness for more than a few days and excretes amylase abnormally 7-10 days after his serum concentration has returned to normal.

No systematic attempt was made to correlate urinary excretion of amylase with symptomatology or other measures of activity as the study progressed. However, when the serial data were plotted and studied in relation to the hospital course, the correlation was surprisingly good despite the lack of detail in the clinical records. In Cases 6 (1955 admission), 10, 11, and 13 minor recrudescences of urinary amylase abnormality correlated well with such signs of activity as the white blood cell count, the

sedimentation rate, and the presence of fever. In Cases 1, 15, 16, 18, 19, and 20 the degree and duration of abnormality of the urinary amylase correlated well with the clinical course as a whole, being reminiscent of a patient (Case A. A.) reported by Stocks [11] in 1916. No such correlation between clinical course and serum amylase concentration was evident.

An incidental observation of some importance because of its frequency in our small group of patients concerns the hazards of manipulative procedures in patients with acute pancreatitis who have but recently become asymptomatic. Two patients (Cases 5 and 20) who had become asymptomatic and who had pseudocysts which were no longer palpable went into shock due to hemorrhage following abdominal manipulative x-ray studies and required emergency exploration. Another patient (Case 1) was explored for a severe recurrence of pain following a gastrointestinal series. Five other patients (Cases 10, 11, 14, 15, and 19) had mild recrudescences of activity following manipulative x-ray procedures or premature institution of oral feedings. The healing process in acute pancreatitis cannot be rushed, and complete rest for the gland is essential. The inflamed gland is particularly sensitive to the slightest trauma, and manipulation of any kind should be delayed until a liberal interval following the complete subsidence of the process has elapsed. The duration of this interval will vary somewhat, depending upon the severity of the episode. However, in the typical attack it should probably be two or three weeks at least.

One additional incidental observation of note is the finding of pancreatitis as a manifestation of leptospirosis in Case 4. Though abdominal pain is a frequent finding in this illness, pancreatitis has not generally been included as a manifestation. It would be of interest to study urinary amylase excretion in an unselected group of such patients.

Summary

Simultaneous serial observations of serum amylase concentration and urinary amylase excretion were made in 19 patients without evidence of renal dysfunction who had 21 episodes of acute pancreatitis, in 1 patient with sialitis, and in 2 patients with renal insufficiency.

In the absence of renal insufficiency, the urinary excretion rate was always abnormal when the serum concentration was abnormal, and the relative degree of abnormality was greater for the urinary values as a rule. In each of these patients the urinary excretion was abnormal one or more times when a simultaneous serum value was normal. All told, the urine value was abnormal 83 times when the serum concentration was normal. In no instance was the serum concentration abnormal when the urine was normal. The serum concentration usually returned to normal within three or four days, however, the urinary excretion generally remained abnormal 7 to 10 days longer. In one patient with a pancreatic cyst containing over 25,000 units of amylase per 100 ml., the daily urine excretion remained abnormal at least six weeks after the serum concentration had returned to normal.

The urinary amylase excretion reflected the clinical course of the patient much more adequately than the serum concentration.

The hazards of manipulative x-ray procedures before the pancreatitis subsides completely or of premature institution of oral feedings were strikingly demonstrated by the occurrence of serious complications in 3 and of minor recrudescences in 5 of the 19 patients with acute pancreatitis.

Acute pancreatitis occurred as a manifestation of leptospirosis in one patient.

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Bacteremia Due to Diplococcus Pneumoniae Associated with Disease of the Biliary Tract

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Bacteremia due to Diplococcus pneumoniae frequently occurs during the course of pneumococcal pneumonia, particularly when the infection is fulminating. Endocarditis, most commonly involving the aortic valve, may complicate pneumococcal pneumonia and is characterized by persistent pneumococcal bacteremia. In pneumococcal meningitis at least 50% of patients have bacteremia due to D. pneumoniae.[1] However, invasion of the blood stream by pneumococci in the absence of pneumonia, endocarditis, or meningitis is unusual.

On the addition of whole bile or bile salts, pneumococci autolyze with great rapidity, and clearing of a turbid suspension of organisms occurs within a matter of minutes. The phenomenon of bile solubility is due apparently to activation of autolytic enzymes of the pneumococci by the bile. If the enzymes are first inactivated by heating the suspension of cocci to 65 C for 30 minutes, autolysis no longer takes place when bile is added.[2]

An infected biliary tree is not a rare portal of entry for certain organisms which invade the blood stream,[3] but invasion of the biliary tree by pneumococci is an extremely unusual clinical finding, apparently because of the bile solubility of the organisms.

It is apparent that disease of the biliary tract associated with bacteremia due to D. pneumoniae raises many interesting questions. We are presenting two cases which appear to represent such coincident unusualities.

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Report of Cases

CASE 1.—A white man, 50 years of age, was first seen at the Mayo Clinic in August, 1946, with the chief complaint of epigastric pain of three months' duration. The patient related that in 1943 he had had intermittent bouts of chills and fever and was suspected of having acute cholecystitis. At laparotomy, stones were found in the gallbladder, and cholecystectomy was performed; a T-tube was inserted in the common bile duct and left in place for nine months. In that same year glycosuria was detected and the blood sugar was found to be elevated. Estimations of the fasting blood sugar had been made at monthly intervals since that time; use of insulin had not been recommended.

One year after cholecystectomy the patient began to have recurrences of fever but had not had further chills. At that time exploration of the common bile duct resulted in removal of a stone. A T-tube was reinserted in the duct and left in place for four months. From that time (1944) until May, 1946, he had felt generally well.

Three months prior to his visit to the clinic the patient had had a recurrence of fever (101 to 102 F) and intermittent epigastric pain extending around the right costal margin to the back. The fever had been present daily and had subsided only after a course of penicillin. However, it had recurred shortly after administration of penicillin was discontinued. He recalled a striking resemblance between his present abdominal pains and the distress experienced prior to removal of the stone from the common duct in 1944. No jaundice had been noted by either the patient or his wife, but the stools had been clay colored for the preceding three months. He had lost 25 lb. since June, 1943.

Positive findings on physical examination included the general impression of a man with a long-standing illness, a liver which was palpable and tender, and a small incisional hernia.

Pertinent data found on initial laboratory examinations included a concentration of hemoglobin of 12.5 gm. per 100 cc. of blood and 3,550,000 erythrocytes and 12,200 leukocytes per cubic millimeter of blood. A differential count of leukocytes revealed 63% neutrophils, 26.5% lymphocytes, 10% monocytes, and 0.5% eosinophils. Results of the flocculation test for syphilis were negative. The only abnormality revealed by urinalysis was glycosuria. A test for acetone in the urine showed positive results, but diacetic acid was not detected. Roentgenograms of the thorax, abdomen, and upper portion of the gastrointestinal tract were considered to be within normal limits. Estimation of the fasting blood sugar revealed it to be 235 mg. per 100 cc. of blood. The concentration of direct reacting bilirubin was reported as 0.7 mg., and the indirect bilirubin as 0.9 mg. per 100 cc. of serum. There was no retention of bromsulphalein in the serum one hour after the administration of the dye in amounts of 5 mg. per kilogram of body weight. The sedimentation rate of erythrocytes was 93 mm. in one hour (Westergren method). Estimation of the serum amylase was within normal limits.

On the eighth day after admission to the clinic, the patient suffered a sudden shaking chill and was found to have a fever (103 F). Thereafter the patient continued to suffer recurrent chills and fever, with temperatures ranging up to 104.2 F. Since the patient was certain that his febrile episodes in the past had responded to administration of penicillin, after three consecutive cultures of the blood were obtained, aqueous crystalline penicillin in amounts of 20,000 units was given by the intramuscular route every three hours. The blood cultures subsequently were reported as yielding D. pneumoniae, approximately 500 colonies per cubic centimeter, and the organism was reported to be sensitive on testing, in vitro, to 0.1 unit of penicillin per milliliter. Two days after instituting therapy with penicillin, the patient's temperature was normal and remained so. Blood cultures obtained after the subsidence of fever were reported as negative.

The clinical impression was definite that the manifestations of infection were coincident with intermittent blockage of the common bile duct and that the bacteremia was secondary to such obstruction. It was deemed wise to explore the common bile duct, but with subsidence of fever the general status of the patient improved, and he elected to defer the procedure. Abdominal exploration was carried out elsewhere a short time later, and inoperable carcinomatous obstruction of the common bile duct was described.

CASE 2.—A 60-year-old white man was first seen at the Mayo Clinic in August of 1943 with the chief complaint of abdominal pain and jaundice. Three years previously the patient first suffered pain in the right upper portion of the abdomen. The pain recurred frequently and was often rather severe. One year after onset of pain, jaundice developed, and, because of this complication, abdominal exploration and cholecystoduodenostomy were performed. Gallstones were not found at this exploration. After operation he had felt relatively well until the winter of 1942, when he began to have recurrence of the pain in the right upper part of the abdomen associated with fever and a shaking chill two to three times weekly. About seven weeks prior to his admission to the clinic the patient had become visibly jaundiced. Physical examination revealed a mildly icteric, very thin man whose upper abdominal region was rather tender and whose liver descended 2 in. (5 cm.) below the right costal margin on deep inspiration and was very tender along the edge.

The clinical impression was that of partial obstruction of the common duct, and laboratory data were confirmatory. The serum bilirubin was elevated, with a reading of 2.1 mg. of direct-reacting serum bilirubin and 0.3 mg. of indirect-reacting serum bilirubin. The patient underwent abdominal exploration. The wall of the gallbladder was inflamed and edematous. Between the upper end of the gallbladder and the common duct was a small localized abscess. The distal end of the common duct was partially constricted. The bile in the proximal portion of the common duct was under greatly increased pressure, and many small stones were encountered therein. Cholecystectomy was performed. Because the stricture of the common duct was felt to be on an inflammatory basis, a reconstructive operation on the duct was done over a No. 18 F. catheter. This catheter was sutured in place. The patient made an uneventful recovery from the operation and was dismissed from the hospital on the 16th postoperative day.

The patient was readmitted to the clinic in March, 1944, at which time he reported that he had been well until January of that year, when recurrence of fever, chills, pain in the same part of the abdomen, jaundice, and mild pruritus developed. At that time he had remained ill for four days, after which the symptoms had subsided only to recur one week before his present admission.

On physical examination positive findings included a liver palpable 5 fingerbreadths below the right costal margin, jaundice, ascites, and splenomegaly. Physical examination of the thorax was within normal limits.

Laboratory data included negative results of urinalysis except for the presence of bile, a concentration of hemoglobin in the blood of 11.0 gm.

per 100 cc. and 3,870,000 erythrocytes and 17,400 leukocytes per cubic millimeter of blood. A differential count of the leukocytes revealed 86.5% neutrophils, 10.0% lymphocytes, and 3.5% monocytes. Roentgenograms of the thorax revealed elevation of the right hemidiaphragm and some haziness in the right lower lung field. Direct-reacting bilirubin per 100 cc. of serum measured 48.6 mg., and indirect reacting, 2.7 mg.

The patient continued to have recurrent chills and fever with temperatures up to 105 F; cultures of the blood were reported as growing D. pneumoniae, Type VI, with five colonies per cubic centimeter. Sulfadiazine was administered by the oral route.

For 48 hours after admission the patient appeared to be improving. Thereafter, the patient's course was progressively downhill. Percussion of the right lower region of the thorax elicited flatness, and over the same area there was great diminution in breath sounds. The patient's abdomen became distended, tympanitic, and generally rigid. There was decrease in the peristaltic sounds, but the patient had noted slight flatus. On the sixth day after admission, oliguria suddenly became evident, and the patient excreted only 15 cc. of urine in 24 hours. At this time there was 120 mg. of urea per 100 cc. of blood. It was conjectured that, since there was an absence of sulfonamide crystals and only a rare erythrocyte on microscopic examination of the urine, the oliguria represented so-called hepatorenal failure rather than sulfadiazine nephrotoxicity. The patient was given penicillin intravenously terminally, but it is doubtful that he received more than 40,000 units in all.

Fig. 1.—Dilated ducts and small abscesses appearing on cut surface of liver.

Fig. 2.—Terminal portion of common bile duct and papilla of Vater. There is a small carcinoma about 2 cm. proximal to the orifice of the papilla.

Necropsy.—Icterus, Grade 3 on a grading basis of 1 to 4, was noted. The peritoneal cavity contained approximately 1000 cc. of bile-stained fluid, and the right pleural cavity contained 500 cc. of cloudy bile-stained fluid. The lungs were not remarkable except for atelectasis of the right middle lobe and atelectasis, edema, and congestion of the lower lobes. The spleen was enlarged and weighed 447 gm. (normal, 150 gm.).

The liver weighed 3383 gm. (normal, 1800 gm.). The tannish-brown surface was studded with small raised white nodules that varied in size up to 1 cm. in greatest diameter. On section some of them were found to contain a purulent exudate. The liver was cut, and the intrahepatic bile ducts were observed to be extensively dilated (Fig. 1). The common bile duct contained a rubber catheter, which extended into the duodenum. The duct was patent and greatly dilated. It contained a mixture of mucopurulent exudate and bile, and acute suppurative cholangitis was evident. The wall of the duct was interrupted in its middle third over a distance of about 2 cm. In this region plastic repair had been performed by utilization of the surrounding soft tissues. In the lower third of the duct there was a small flat nodule, about 1 cm. in length, which encircled and appeared to infiltrate the wall of the duct (Fig. 2).

The esophagus revealed evidence of pseudomembranous and ulcerative esophagitis. The stomach was dilated and contained 500 cc. of bile-stained fluid; multiple petechial hemorrhages were

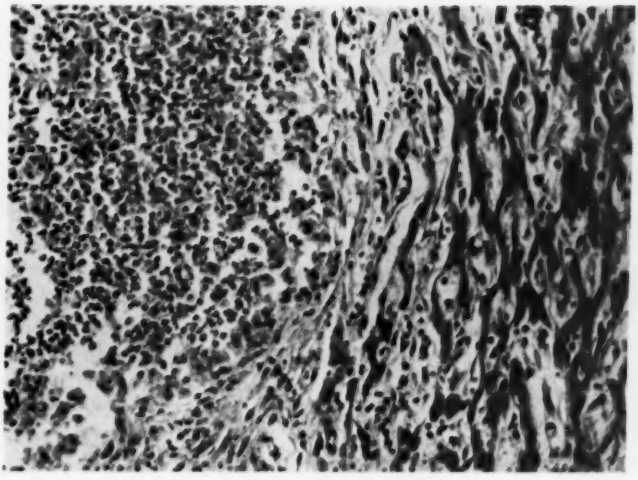

Fig. 3. — Section of liver showing evidence of abscess; hematoxylin and eosin; × 190.

noted in the mucosa. The duodenal mucosa was congested in the region of the papilla of Vater. A superficial ulcer measuring 0.5 cm. was found at the anal margin of the rectum. The kidneys weighed 549 gm., compared with an estimated normal weight of 275 gm.

Histologic Examination.—Small foci of bronchopneumonia were present in the right middle lobe and the left lower lobe of the lungs. Both lower lobes showed evidence of edema and collapse. The spleen was congested and contained increased numbers of polymorphonuclear cells in the pulp and sinuses. The liver revealed increased fibrous connective tissue and large numbers of polymorphonuclear cells in the periportal spaces. Polymorphonuclear leukocytes also were observed in a few interlobular bile ducts. There were multiple abscesses of varying size in the liver. The small abscesses appeared to be in close relation to the periportal spaces, whereas the large ones had extended into the lobule (Fig. 3). Sections stained by the Brown-Gram technique revealed large numbers of Gram-Positive diplococci. In addition there was evidence of chronic passive congestion with atrophy of hepatic cells in the central portions of the lobules. The Kupffer cells in these latter regions contained a yellowish-brown pigment.

Sections of both hepatic ducts revealed sloughing of the epithelium and purulent exudate in the lumen. In the common bile duct an adenocarcinoma, Grade 2, infiltrated the wall. In addition to the carcinoma, necrotic tissue with a collection of polymorphonuclear cells was present in the intramural portion of the duct.

The collecting tubules and loops of Henle contained pigmented granular material. Focal and diffuse collections of interstitial lymphocytes, plasma cells, and a few polymorphonuclear cells were observed. These cells were most prominent at the corticomedullary junctions.

The following anatomic diagnoses were made: Carcinoma of common bile duct; dilatation of hepatic ducts with acute suppurative cholangitis and multiple abscesses of the liver; acute interstitial nephritis with lower nephron nephrosis; congestion, edema, and atelectasis of lower lobes of lungs; focal bronchopneumonia.

Comment

Infection of the biliary system due to pneumococci is rare, and we were able to find only sporadic mention of this association in the literature. In 1934 Mendonça Cortez [4] reported the case of a patient who had had acute cholecystitis, and at operation the contents of the distended gallbladder were found to include large numbers of pneumococci on direct smear. The identity of the organisms was confirmed by culture. The patient died a few days after the cholecystectomy. The author, in his comments, emphasized the extreme rarity of pneumococcal cholecystitis.

Brown and Lockhart [5] reviewed pneumococcal infections of all types which had occurred in adult persons at the San Francisco Hospital during the years 1932 to 1946, inclusive. They found 1562 patients in that broad general category, and among them there was only one person in whom the

diagnosis of pneumococcal cholecystitis had been substantiated. In this instance the infection was caused by pneumococci, type XVII.

The rare association of infection of the biliary tract by pneumococci has been attributed to concepts based on the original work of Neufeld.[6] Neufeld first observed in 1900 that pneumococci underwent lysis in bile.[6] The thesis has been advanced that the ability of bile to induce autolysis of the organisms ordinarily militates against their invasion of the biliary tree. Neufeld, in his original publication, mentioned that he had encountered one strain of D. pneumoniae which was not autolyzed by bile. Farah[7] also pointed out that certain strains of pneumococci are not dissolved by bile. Thus it is possible, theoretically at least, that when pneumococci have succeeded in invading the biliary tree they represent these strains which are not autolyzed by bile. The observations on the bile solubility of pneumococci were the basis for enthusiasm generated among clinicians early in the present century about treating pneumococcal infections with bile salts. To cite one report, bile salts were instilled in pleural cavities of patients with pneumococcal empyema.[8] Others administered bile salts by the intravenous route in cases of bacteremia due to pneumococci.[9]

Our first patient had exhibited a fever for several months prior to his coming to the clinic. He had noted that his fever subsided each time he took penicillin, and on discontinuance of the antibiotic, the fever had recurred. Once the bacteriologic diagnosis of the infection in his blood stream was established and he was treated more vigorously with penicillin, the process apparently subsided. At no time during the patient's stay in Rochester was there clinical or roentgenographic evidence of pneumonia.

The second patient had a more fulminating infection, apparently. Terminally equivocal physical signs of consolidation developed in the right lower lung field, but these might have been accounted for by the elevation of the right hemidiaphragm or by contiguous spread of the inflammatory process. Bacteriologic examination of specimens of sputum did not reveal evidence of pneumococci. Similarly, gross and microscopic examination at necropsy showed congestion and edema in both lower lobes and only small foci of pneumonia that was probably a terminal development. In any event the general infectious process, including the bacteremia, antedated any clinical evidence of possible pneumonitis.

While bacteriologic proof that cholangitis was the precipitant of the pneumococcal bacteremias is lacking, it appears legitimate to suspect strongly that the association was more than coincidental. In any event one probably has to conclude that either these two patients were victims of primary pneumococcal bacteremias, or they were afflicted with an even more rarely encountered sequence of events wherein pneumococcal infections of the biliary tree served as portals of entry for the bacteremias.

It is interesting that in both cases a carcinomatous lesion obstructed the common duct. These cases point up a well-known clinical observation: that cholangitis is secondary to an obstructing lesion.

Summary

Invasion of the blood stream by pneumococci in the absence of pneumonia, endocarditis, or meningitis is unusual.

Two cases of disease of the biliary tract associated with bacteremia due to Diplococcus pneumoniae are presented. The pertinent literature is reviewed, and some of the theoretical aspects of this unusual association of diseases are discussed.

Mayo Clinic, Section of Medicine.

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Emotional Factors in Coronary Occlusion

1. Introduction and General Summary

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"Stress and strain" are regarded by the laity and the medical profession alike as an integral part of the problem of coronary occlusion, but medical observations concerning these factors have been focused chiefly on physical exertion. Except for a few case reports, very little effort has been made to conduct systematic studies from a psychosomatic standpoint. Perhaps the organic tradition in medicine has encouraged us to think of coronary occlusion as a "purely physical disease," with emphasis on heredity, dietary factors, and easily demonstrable coronary atherosclerosis; but the frequent onset of coronary occlusion during sleep or rest has also inclined observers to minimize emotional stress. Perhaps, too, the unwillingness to attempt psychiatric interviews with a very sick patient is another reason for the failure to study coronary occlusion from an emotional standpoint. Emotional factors have also been neglected in regard to treatment; physical rest and physical measures have been emphasized.

We do not wish to minimize the preexisting coronary artery disease that is the essential background for coronary occlusion. However, it has been demonstrated that emotional stress may be accompanied by measurable changes in pulse rate, stroke volume, cardiac output, peripheral resistance, and arterial blood pressure.[1-4] Clotting time and blood viscosity may also be influenced by emotional stress,[5] so apparently physiologic changes may be brought about that increase the work of the heart and impair its efficiency. Thus emotional factors might conceivably add to the burden of an impaired coronary circulation. However, we have not concerned ourselves with the study of these mechanisms but rather with an effort to determine the incidence and possible significance of emotional factors in a group of patients with myocardial infarction following coronary occlusion compared with a control group of patients who presented no evidence of coronary artery disease. The possibility that emotional stress may be one of the aggravating or contributing factors as well as the role that the emotions may play in the reaction to the illness and in recovery have been of interest to us.

Review of Literature

A few individual cases and only an occasional small series of patients with coronary artery occlusion have been studied from a psychological standpoint. Dunbar,[6] in a psychiatric study of 22 patients, described a typical personality profile, and Arlow[7] also found a clear-cut constellation of personality traits in patients with coronary artery disease. Both found evidence for compulsive competitive striving and concluded that the character structure of the patient predisposes him to coronary occlusion. Dunbar referred to the "coronary personality" as consisting of "compulsive

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striving, hard work, self-discipline, and great need to get to the top." Both emphasized the psychodynamic importance of the patient's childhood conflicts with authority. Arlow described an early competitive relationship with a much feared and envied parent (usually the father). He stated that the characteristic defense mechanisms used in dealing with this focal conflict were repression and identification, but that they served their purposes inadequately because the patient continued to reexperience his old conflict with authority over and over again as he unconsciously recreated in new forms the original situation of competition. He drove himself compulsively, through hard work and self-discipline, but success brought no sense of gratification or relief from tension.

Cathcart,[8] a Canadian psychiatrist, was impressed with emotional factors in the precipitation of coronary occlusion in a series of patients whom he had seen in consultation, and in a study from a Finnish hospital, Järvinen [9] concluded that some patients developed coronary occlusion while in the hospital from the emotional stress associated with ward rounds. Van Balen [10] also studied a small series of patients and called attention to the fact that psychological factors may remain unrecognized unless a special inquiry is made with regard to this possibility.

Most of the large-scale studies on coronary occlusion by cardiologists minimize the importance of emotional factors in coronary occlusion. Master and Jaffe,[11] studying the factors in the onset of coronary occlusion and coronary insufficiency, amassed a good deal of evidence to show that coronary occlusion is not brought about by events in the external environment. In their large series they found that about half of the attacks began during sleep and rest, and since the majority of persons spend half the day in this way these activities may be considered coincidental. Similarly, they conclude that the association of only 2% of the coronary occlusion attacks with severe exertion is also coincidental. They argue that most persons perform some unusual effort at least several times a day, so, if effort were a precipitating factor in coronary occlusion, the incidence of attacks during strain should be much greater. Even when coronary occlusion seemed to follow directly after effort, they call attention to the fact that coronary thrombosis takes place over a variable period, occasionally several weeks prior to the attack, so that the occlusion had already completely formed. Therefore while "exertion may account for the appearance of symptoms and even death, it does not account for the coronary occlusion that had occurred spontaneously." Very little attention is paid to the question of emotional stress, and this is generally true in papers dealing with the onset of coronary occlusion and in chapters on this subject in textbooks of medicine and cardiology. For example, Ancel Keys, long a protagonist of the nutritional approach to atherosclerosis, in speaking of coronary heart disease and the mode of life comments, "Other factors beside the diet need more attention but it is fair to say that, except for physical exercise, no other clue is in sight. Even the concept that 'stress and strain' is influential needs study because of the complete absence of evidence for its validity."[21]

Nevertheless, there has been an important contribution to this subject. Miles, Waldfogel, Barrabee, and Cobb,[12] studied 46 patients selected from the clinical material utilized by Gertler and White [13] in their study of coronary heart disease in young adults. Miles et al. were interested in the relation of personality factors to the genesis of atherosclerosis of the coronary arteries. Their study was made on an average of 5.6 years after the attack of coronary occlusion, so that it differs from ours in this respect as well as the fact that it was done on 46 young men with coronary artery disease (average age 41.7 years) and was controlled by a study of 49 healthy men (average age 39). A complete psychosocial survey was made, with special effort to see whether the coronary personality as described by Dunbar

and Arlow could be confirmed. They could find no convincing evidence that the personality exhibited by the coronary patient, as compared to the control subject, could be implicated as a significant factor in the genesis of coronary artery atherosclerosis. "The coronary patients had tended to work harder, under more stress and strain, although this was not necessarily physically strenuous work. Only a few more of the coronary patients than controls showed a consistent tendency toward compulsive striving, ascetic self-discipline, and greater need to 'get to the top' in their chosen work. When the two groups were compared in terms of specific personality traits, the differences were very slight. The coronary group showed less tendency to introspection than did the controls and more difficulty in handling their aggressive tendencies. The similarities between the groups were more striking, however, than were the differences, and our findings, in the main, did not confirm previous observations."

Miles et al. assume that acute coronary occlusion with myocardial infarction can be precipitated by severe emotional stress, but they did not concern themselves with this question and were only interested in the causal relationship that may exist between personality factors and coronary artery atherosclerosis.

Another excellent study related to ours has to do with emotional stress in the precipitation of congestive heart failure. Chambers and Reiser[14] studied 25 consecutive patients admitted to the Cincinnati General Hospital with heart lesions representative of those usually seen in a large city hospital (hypertensive, atherosclerotic, rheumatic, syphilitic, etc.). It was found in this series that emotional factors had played a major precipitating role in 19 of the patients (76%). While all of these 19 patients had been living under severe chronic emotional strain, in each of them the superimposition of an acute, emotionally stressful experience appeared to be the factor immediately responsible for the onset of cardiac decompensation. They were precisely the type of patients in whom the possibility of an emotional component in the illness is usually minimized or ignored by medical teachers and practitioners. They also comment on certain reactions to heart disease such as "denial of illness" to which we will refer.

Chambers and Reiser go on to say, "The observations summarized above on congestive heart failure, have not been matched by comparable studies on myocardial infarction. There are many case observations, but as yet no systematic studies, which would indicate that myocardial infarction, like congestive failure, may be precipitated by emotional turmoil."

Methods and Material

In 43 patients suffering from myocardial infarction who were admitted to the Temple University Hospital beginning in the fall of 1953, an effort was made to study the personality structure and life situation in an attempt to determine the role of emotional factors on the onset, course, and recovery from coronary occlusion. We tried to study consecutive cases but were not always successful in this endeavor. We could not always obtain permission from the physician in charge of the case; the patient was occasionally too ill to be studied at the time the psychiatrist was available, and we could not always find time to study the number of cases that were available. None of our own cases were included.

In addition to the usual physical studies and medical management the patients were interviewed by psychiatrists. The interviews were begun as soon as the patient was comfortable enough to discuss himself freely—on the average the first one took place nine days after admission to the hospital—and varied from 3-12 in number, averaging 7 per patient of about an hour each. The interviews were conducted at the bedside.

An equal number of hospital patients, matched for age, sex, and race, served as controls. Patients with coronary artery disease were excluded as well as those with obvious mental, nervous, and psychosomatic disorders.

The selection of control cases in psychosomatic investigation is always a difficult problem. For example, the high incidence of social and emotional problems in a hospital ward population is one such complicating factor. Miles et al. comment upon the problem of controls in the paper

to which we have already referred, stating that "controls" are impossible to keep "controlled" and that the personality and theoretical convictions of the investigator inevitably influence the making of discriminating observations and the drawing of inferences.

We also felt that interviews were liable to be biased, especially when the diagnosis was known, so we tried to protect ourselves in this respect by weekly group conferences in which the material was reviewed and conclusions reached.

The interviews were conducted by dynamically trained psychiatrists along the general lines of psychiatric interviewing and without special emphasis on any particular affect or personality traits. The patient was told that the interviewer was a psychiatrist, working with the physician in charge of the case, interested in the study of emotional factors in heart disease. Whenever possible other members of the family were also interviewed, particularly the spouse, and a great deal of helpful information was obtained in this way.

The age distribution of our cases (Table 3 and Fig. 1) corresponds to that found in other studies and the number of cases occurring during rest and sleep (almost half) (Table 4) also correspond with other studies. The occupational breakdown (Table 5) corresponds fairly well with that of Miles et al., except that they had a somewhat larger percentage in the professional and executive group. The percentage of Jews in our group is the same as Miles et al. (Table 6). They have referred to the fact that the percentage of Jews in the Dunbar study (59%) may have influenced her findings in respect to a "coronary personality," but since the percentage of Jews in our group was the same as in the study by Miles et al., it does not seem likely that this factor influenced our results in relation to theirs. More will be said on this subject later.

Therefore, while our series is small, it seems to be representative. The diagnoses varied in the control group (Table 2). In the occupational breakdown (Table 5) it will be noted that Classes 3 and 4, representing the majority of cases, nearly equal one another in the coronary and control groups. There are more ward patients among the control group (Table 7), 23 as opposed to 10; more Catholics among the controls (16 to 8), and more Jews among the coronary group (15 to 5).

TABLE 1.—*General Summary—Coronary Cases* *

Case	Age	Sex	Race	F.H.	O.	P.C.V.D.	A.	G.M.T.	A.E.S.	A.D.
1	59	M	W	+					+	
2	67	M	W		+		+		+	Diabetes
3	54	M	W	+				+		
4	47	M	W		+		+	+		
5	51	M	W		+	+		+		
6	56	F	W			+			+	
7	58	F	W		+					
8	43	M	W					+		
9	67	M	W					+		
10	43	M	W	+		+	+		+	H.C.V.D.
11	33	M	N					+	+	
12	41	M	N	+	+	+				Chronic glomerulonephritis
13	62	M	W	+		+		+		
14	48	M	W	+		+	+	+		
15	72	F	W			+			+	H.C.V.D.
16	75	M	W						+	Atherosclerosis
17	48	M	W	+	+					
18	70	F	W						+	
19	55	M	W	+		+		+	+	
20	41	M	W	+		+		+		
21	72	F	W	+		+				
22	44	F	N		+			+		Toxic goiter
23	62	M	W			+				
24	49	M	W						+	
25	49	M	W	+				+		
26	59	M	W	+		+		+		Diabetes
27	40	M	W		+	+		+		
28	44	M	W			+		+		
29	52	M	N			+	+			Syphilis
30	42	M	W					+		
31	61	M	W		+	+				Diabetes
32	54	M	W	+		+		+	+	
33	78	F	W		+	+			+	
34	47	M	N					+		
35	49	M	W		+				+	
36	38	M	W	+				+		
37	62	F	W	+			+		+	
38	67	M	W	+		+			+	
39	60	M	N	+						
40	57	M	W			+		+		
41	42	M	W					+		Diabetes
42	50	M	W	+		+				
43	48	M	W			+			+	

* F. H. indicates family history; O., obesity; P.C.V.D., previous cardiovascular disease; A., physical activity; G.M.T., gradually mounting tension; A.E.S., acute emotional stress; A.D., associated diagnoses.

TABLE 2.—*General Summary—Control Cases* *

Case	Age	Sex	Race	F.H.	O.	P.C.V.D.	A.	G.M.T.	A.E.S.	Diagnosis
1	66	M	N	+	−	−				Carcinoma, esophagus
2	42	M	W	−	−	−				Traumatic stenosis, larynx
3	41	M	W	+	+	+				Tracheobronchitis, H.C.V.D.
4	50	M	N	−	−	−				Carcinoma, left bronchus
5	72	F	W	−	+	−				Fracture, left intertrochanteric
6	65	M	W	−	+	−				Hemorrhoids, diverticulosis
7	62	M	W	+	−	−				Tuberculosis, pulmonary (active) (moderately advanced)
8	40	M	W	−	−	−			+	Kyphosis, scoliosis
9	68	M	W	−	−	−				Prostatic hyperplasia, benign
10	41	M	N	−	−	−				Epidermoid cyst, neck
11	43	M	W	+	−	−				Carcinoma, right lung
12	61	F	W	−	−	−				Carcinoma, rectosigmoid
13	32	M	N	−	+	−				Diabetes
14	73	F	W	+	−	−			+	Fracture, right intertrochenteric
15	41	F	N	−	+	−				Leiomyoma, uterus
16	56	M	W	−	−	−			+	Fracture, pubis
17	70	F	W	−	+	−				Burn, left leg, 2d degree
18	42	M	W	−	−	−				Paget's disease, fractured T_{12} acute
19	39	M	W	−	−	−			+	Leukemia, myelogenous
20	63	M	W	+	−	−				Cholecystitis, calculous
21	50	M	W	+	−	−				Paget's disease
22	42	M	W	−	−	−				Hemorrhoids
23	48	M	W	+	−	−				Burns, right hand, 3d degree
24	65	F	W	+	−	−				Carcinoma, metastatic; diabetes
25	63	M	W	−	+	−				Prostatic hypertrophy, benign
26	65	M	W	−	−	−				Emphysema, right lung, compensatory
27	54	M	W	−	−	−				Melanoma, malignant
28	54	M	W	−	−	−				Carcinoma, bronchogenic
29	40	M	W	−	−	−				Osteomyelitis chronic, left femur
30	42	M	W	+	+	−				Fractured tibiae, right and left
31	53	M	W	−	−	−				Hernia, inguinal
32	45	M	W	−	+	−				Diabetes
33	39	M	W	−	−	+				R.H.D. with mitral valvulitis; psychoneurosis, mixed
34	47	M	W	−	−	−				Fractured cervical vertebra
35	54	M	W	−	−	−				Prostatic hyperplasia, benign
36	50	M	W	−	+	−				Urinary tract, diagnostic problem
37	57	M	W	−	−	−				Hernia, inguinal, direct right
38	58	F	W	−	+	−				Ovarian cystadenoma
39	46	M	N	+	−	−				Hemorrhoids
40	60	M	W	−	−	−				Hernia, inguinal, right
41	58	F	W	−	+	−				Uterine prolapse
42	43	M	W	−	+	−				Bronchiectasis
43	75	M	W	−	+	−				Tuberculosis, pulmonary

* F.H. indicates family history; O., obesity; P.C.V.D., previous cardiovascular disease; A., physical activity; G.M.T., gradually mounting tension; A.E.S., acute emotional stress.

Results

Family History.—A family history of heart disease occurred in 19 (44%) of the coronary group and 14 (32%) of the control group (Table 8), but psychopathology existed in the background of 20 members (46%) of the coronary group, as opposed to 7 (16%) in the control group. Psychopathology refers to obvious mental or nervous illness or to evidence of pronounced emotional maladjustment.

Past History.—Preexisting cardiovascular disease occurred in 22 (51%) of the coronary artery group but in only 2 (5%) of the control group (Table 1). Angina was present in 11, hypertension in 6, and previous infarction in 5.

Physical Stress.—Physical stress seemed to precede coronary occlusion in six patients (14%) (Table 4). It was not evaluated among the controls.

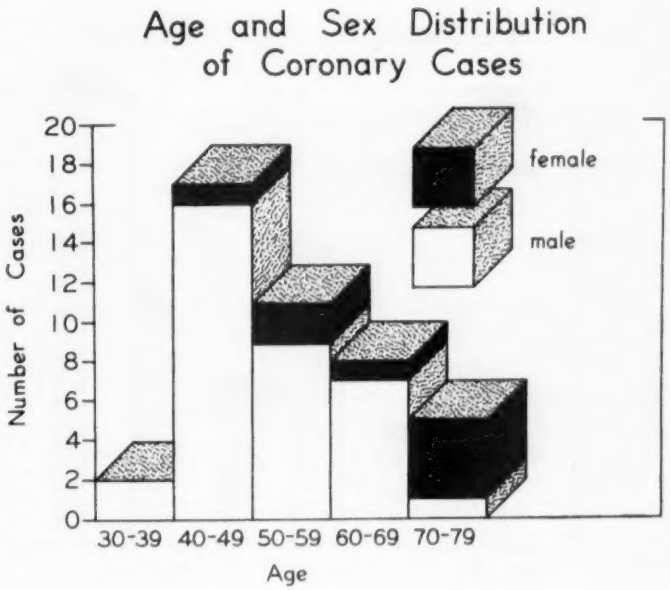
TABLE 3.—*Age Distribution of Coronary Cases*

Age	Men		Women	
	White	Negro	White	Negro
30-39	1	1		
40-49	14	2		1
50-59	8	1	2	
60-69	6	1	1	
70-79	1		4	

TABLE 4.—*Time of Attack*

	Coronary	Control (not evaluated)
Sleep	12	
Resting	9	
After meal	4	
Usual activity	12	
Increased activity	6	

Figure 1



Psychological Classification.—The diagnosis of neurosis was established when the patient gave a history of symptoms of emotional origin that interfered with his relationship with other people or seriously impaired his capacity to work. This diagnosis was established in 10 (23%) of the coronary group, as opposed to 6 (14%) in the control group (Fig. 2).

Character disorder was diagnosed when rigid and repetitive behavior interfered with the person's happiness and the security of his family. The neurotic character "acts out" his impulses; symptoms of emotional origin are few or absent. Eighteen (42%) of the coronary group fell into this classification and only nine (21%), in the control group. This difference is statistically significant ($P<0.01$).

TABLE 5.—*Occupation*

	Coronary	Control
Class 1 (professional and executive)	1	
Class 2 (business and minor executive)	10	1
Class 3 (small businessman and clerical)	20	11
Class 4 (skilled labor)	4	17
Class 5 (unskilled labor)	1	5
Housework	7	7
Retired		1

TABLE 6.—*Religion*

	Coronary		Control	
	Men	Women	Men	Women
Protestant	15	5	16	6
Catholic	6	2	16	0
Jewish	14	1	3	2

Twenty-eight (65%) of the control group were considered well adjusted, but only fifteen (35%) of the coronary group.

TABLE 7.—*Hospital Status*

	Coronary	Control
Ward	10	23
Semiprivate	23	17
Private	10	3

Psychological Stress

Gradually Mounting Tension.—Study of the personality and life situation of patients with acute coronary occlusion compared with a control group showed that gradually mounting tension of emotional origin, months or years in duration, occurred prior to the onset of the occlusion in 21 (49%) of the cardiac group (Table 9). Analyzing the incidence of gradually mounting tension among the different age groups in men we find that it occurred in only 2 out of 8

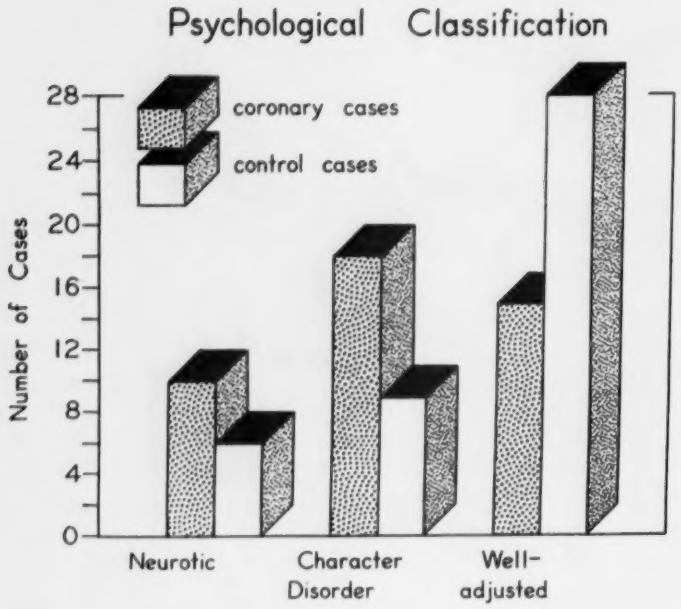


Figure 2

(25%) over the age of 60 but in 18 out of 27 (66%) under the age of 60. The sample is too small for statistical analysis, but the observation may be medically important. We found no evidence of gradually mounting tension prior to the onset of illness in the control group. In addition, 16 (37%) of the coronary group showed acute emotional stress which at least on four occasions (9%) was added to the gradually mounting tension just before the onset of the coronary occlusion. Acute emotional stress existed prior to illness in only 4 (9%) of the control group. This difference is statistically valid ($P<0.05$).

TABLE 8.—*Family History*

	Coronary	Control
Heart disease	19	14
Psychopathology	20	7

TABLE 9.—*Emotional Factors*

	Coronary	Control
Gradually mounting tension	21	
Acute emotional stress	16	4
Anniversary reaction	4	
Anniversary reaction (suspected)	5	

Evidence for gradually mounting tension was not always obvious to the observor, nor was it often apparent to the patient. Sometimes members of the family and especially the spouse helped us in obtaining such information. Increased smoking and drinking (which are sometimes blamed for the coronary occlusion) are often only the evidences of increasing tension of nervous origin. The same is true of irritability and suppressed anger, as well as insomnia, indecisiveness, withdrawal from social contacts, increased dependency on a spouse, obsessive thinking, preoccupation with bodily symptoms, inability to concentrate, disturbances in memory, impotence, depression, and fear of insanity. An example follows.

A white machinist, age 43, was admitted to the hospital following an attack of coronary occlusion. He was a prematurely gray, passive and compulsive person. He had been dominated by his father, also a machinist, toward whom he had been totally submissive, and he had been betrayed by his first wife, who was unfaithful to him. He took great pride in the quality of his work and, when he saw his work being destroyed as a result of the speed-up in the shop, he was filled with rage which he was unable to express. He felt himself heading for catastrophe. There were signs

of mounting tension, such as increased concern about orderliness, neatness, and bowel function, difficulty "getting himself going in the morning," obsessive thinking, and decreased libido.

He described the events leading up to the attack as follows: "Everything had been o. k. at work until the last few weeks. Then they started a speed-up, smashing the equipment and, because of the increased load on the machinery, as fast as we rebuilt it they smashed it again. Work used to be enjoyable but now I hated to get up in the morning. All the knocks I've had in life couldn't add up to this. The job got me down. I took my work home with me. Something had to happen. When I saw my work being smashed to pieces, it broke my heart. This (pointing to his heart) is the result. I couldn't talk to my family about it but I'm glad to get it off my chest."

No other precipitating factors could be demonstrated. There was no evidence of cardiovascular disease in the family history, no obesity, no hypertension or angina, and no hypercholesteremia.

The patient appeared to profit from his interviews and made an uninterrupted recovery from an acute anteroseptal infarction.

Sexual Problems.—The coronary age is also the age of diminishing potency. Sexual problems creating tensions occur, especially among men. Since men are so much more likely to have coronary artery disease than women these tensions are of particular significance. In 21 (49%) of our cases there were important sexual problems and 18 (42%) of these occurred in men. Loss of libido, premature ejaculation, a feeling of "growing old," or the "change of life," preoccupation with the idea of "loss of manhood," and compensatory efforts to prove oneself still a vigorous man (a frequent source of "stress and strain") are some of the problems that afflict men of this age. As previously mentioned in our discussion of evidences of gradually mounting tension, this is just another piece of evidence, but one which is apt to be of greater concern and therefore in itself productive of more tension.

TABLE 10.—*Sexual Problems*

	Coronary	Control
Normal	16	29
Widowed	3	3
Abnormal		
Impotent	10	3
Frigid	2	
Premature ejaculation	1	2
Inadequate outlet	2	1
Total abstinence	2	3
Decreased libido	2	
Excessive sex	1	1
Priapism	1	
No information	3	1

Sexual problems occurred more commonly in the coronary group than in the control group (Table 10 and Figs. 3 and 4),

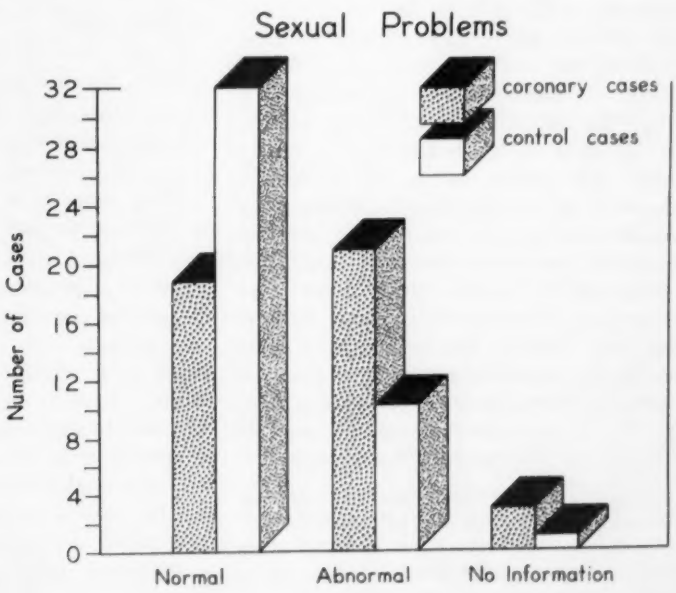


Figure 3

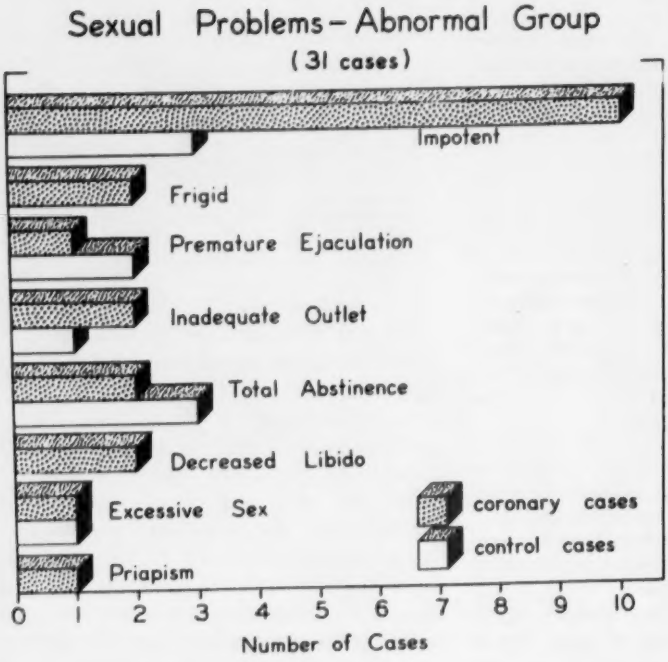


Figure 4

21 (49%) as opposed to 10 (23%). This is statistically significant ($P<0.05$).

*Anniversary Reaction.**—We have been impressed by the fact that the attack of coronary occlusion sometimes seems to occur on the anniversary of a significant event in the life of the patient. This is usually the death of some key figure with whom the patient had established a complex identification in which hostility is usually noted. The patient may be completely unaware of the circumstances, and only when his attention is called to the fact does he recall the anniversary or the tension associated with it. In four (9%) of our cases of coronary occlusion this seemed to be true, and in five others (12%) it seemed a likely possibility, although we could not get enough confirmatory evidence to feel certain about it. There was none among the controls (Table 9). We refer to this phenomenon as the anniversary reaction, but we do not suggest that it is limited to coronary occlusion, because it also occurs throughout the whole field of emotional disorders and psychophysiological reactions.

A story such as this is often obtained. A man approaching his 54th birthday, whose father died at 54 of heart disease, will show increasing evidence of tension, as previously described, and then in response to what seems to be an insignificant event or circumstance will suffer a coronary attack. When queried about any concern or worry prior to the attack he will deny it or refer only to the fact that he had been "overworked." He does not realize the significance of the anniversary of his father's death in regard to his own gradually mounting tension. The psychopathology is usually that of a hostile identification with the dead father. Perhaps the patient has had mixed feelings of respect and devotion but also fear and hostility toward a tyrannical father. He is burdened by

* (Ferenczi[15] credits Freud with the concept of the anniversary reaction. Hilgard[16] used the term in relation to mental illness and Bressler[17] in relation to ulcerative colitis.)

guilt because of hostile feelings which may be wholly unconscious. He begins to believe that he too may die as the father did so that when he approaches the age at which his father died tension increases.

Reaction to Illness

Because of the special significance of the heart the reactions to 'heart attacks" are often unusual. We judged the reaction as normal when the well-adjusted personality reacted with concern and mood changes which, however, gradually disappeared as healing accurred. In 26 (65%) of the known reactions to illness † in our control cases it was regarded as normal or well adjusted, but in only 11 (37%) of our coronary cases did we judge the reaction to be normal (Table 11).

TABLE 11.—*Reaction to Illness*

	Coronary	Control
Normal	11	26
Denial	6	8
Depression	7	1
Regression	2	1
Mixed reaction	4	4
Died	1	
No information	12	3

Denial of Illness.—Denial of illness of varying degree is apt to occur under many circumstances. For example, it is extremely common in malignant disease, but it has special significance when it occurs in heart disease. Chambers and Reiser [14] pointed out that it may have serious implications for the patient with heart disease. It may lead to self-destructive behavior, such as the refusal to accept orders, "forgetting" to take medicine, and pronounced depression. Rigid enforcement of restriction in such patients may cause additional anxiety. They noted that the psychologic need to deny illness was often of such great intensity that it was actually less harmful to permit some activity than it was to impose the degree of inactivity which seemed indicated on the basis of physical considerations alone. In several of their cases it appeared clear that a permissive attitude toward the defense of denial was the best way to manage the patient. This has also been our experience in patients with coronary occlusion.

Incidentally, this points up an interesting observation regarding "clinically important" as opposed to "statistically significant." Eight (20%) of our control cases showed the phenomenon of denial, whereas it occurred in only six (20%) of the known reactions in the coronary group, and yet we felt that denial was more important in the cardiac group, for the reasons stated above, than in the control group, where it was so often associated with the presence of malignant disease (six out of eight cases). Judging the matter only from a statistical standpoint might lead to a dismissal of the importance of denial in the cardiac group if clinical experience is not taken into consideration.[20]

Depression.—Depression is a reactive mood disturbance often accompanied by hypochondriacal concern regarding the heart. It occurred in seven (23%) of our cases, as opposed to only one (2%) in the control group. It has special significance because it can easily be overlooked by the physician who is only concerned about the physical aspects of the heart disease. On the other hand, it can be pronounced enough to mask heart symptoms and thus endanger the patient as well as pose a threat to the psychiatrist.[18]

Regression.—Regression is a phenomenon that may lead to psychological invalidism with hypochondriacal obsession concerning heart symptoms. Passive and dependent character traits are exaggerated, and the patient may become an invalid, perhaps subsisting on insurance benefits. It occurred in two (7%) of the coronary group and in one (2%) of the controls.

The personality and training of the physician are important in regard to the above considerations because by encouraging denial or regression he may add to the patient's problem instead of helping him.

† Since the reaction to illness was not determined in 12 of the coronary cases and in 3 of the controls, percentages will differ in this section.

Comment

Comparing a group of patients with acute myocardial infarction due to coronary occlusion with a control group of patients matched for age, sex, and race with a variety of diagnoses, other than coronary artery disease and obvious mental and nervous ailments, we find a significantly higher incidence of emotional problems in the coronary group. This is especially true of gradually mounting tension and acute psychological stress occurring prior to the onset of the occlusion. It suggests that this may be a factor of importance both in the onset of the disorder and in the reaction of the patient to the disorder.

The Interview.—In the beginning of the study we had some concern that discussing emotional problems with a very sick patient might make him worse, but our apprehensions were somewhat relieved when we found that many patients welcomed the opportunity to talk about themselves and apparently derived great benefit from "getting things off their chests." However, there were many resistances to be overcome, especially in the patients with character disorders, and we were careful to go slowly in our interviewing techniques and observed more than the usual precautions.

Knowing what to talk about or rather what to encourage the patient to talk about is of course the crux of the matter. In criticism of the psychosomatic approach to medical problems doubt is often cast upon the "anecdotal" method of determining the significance of emotional factors. But the anecdote is not an isolated event—it must be related to the total life situation and personality structure of the patient. It is like the question of who is looking through the eyepiece of a microscope in the examination of a pathological specimen. The untrained person sees nothing of significance; the trained person does. The same thing is true in psychopathology. The untrained person can talk to a patient for hours and learn nothing of significance. The physician trained in psychodynamics interviewing a patient will frequently discover that (1) in addition to the chief problem there are other symptoms suggestive of psychosomatic illness; (2) the family history shows a high incidence of psychopathology as does the childhood history; (3) longitudinal study of the life history indicates neurotic personality structure or character disorder; (4) cross sectional study of the life history at the time of the onset of the disorder demonstrates an emotionally disturbing event specific for that particular personality structure; (5) discussing this material brings out meaningful behavior on the part of the patient, and (6) dealing with this material has psychotherapeutic value. However, we must caution that not every physician is prepared to engage in this kind of an investigation and that harm may result if the physician does not understand what he is doing. It also seems likely that not every patient with coronary occlusion should be interviewed even by a properly trained psychiatrist. It is obvious that the patient may be too sick physically to engage in an interview, and he may also be too sick mentally to profit from an interview. This the properly trained psychiatrist can quickly discover. We could find no evidence that the course of the disease had been influenced unfavorably by the interviews. In our series of 43 coronary patients there was only 1 hospital death, and in this patient no therapeutic relationship was established, so we could not relate the death to the interview. On the other hand, we do not wish to imply that lives have been saved by the psychotherapy that is an inherent part of such interviews. While the majority of patients looked forward to the interviews and seemed to derive benefits from them, only the proper study of a larger series for a longer period of time would permit this kind of conclusion. However, it was often striking that the patient who had been put to bed with the enforcement of strict rest and had been cautioned "not to worry" frequently was full of tension and was greatly relieved by

the opportunity of talking about his many problems.

Tension During Rest.—Because coronary occlusion occurs so commonly at rest or during sleep it is assumed that "such patients could not be under strain." It may be quite true that hypodynamic factors are responsible, but it must not be forgotten that tensions also occur during sleep. Grinding of teeth (bruxism) and nightmares are indications of the anxieties that give rise to tension during sleep. Bond [19] called attention to this in recounting the dreams of patients who suffered coronary occlusion during the night. Physical rest is not synonymous with peace of mind; patients may be told to rest (or physical rest may be enforced) and yet they "stew in their own juices," creating tensions that can disturb the circulation.

The "Coronary Personality."—Miles et al. did not find an increased incidence of psychopathology in their coronary group as we did. However, since their study took place with an average interval of 5.6 years after the attack of myocardial infarction, they comment that it was difficult to evaluate the kind of life situation associated with the acute attacks or to estimate the degree of anxiety and depression that had existed immediately after the attack. Nevertheless, they did feel that their coronary patients tended to utilize repression to a notably greater degree than the controls.

While our study was not designed to throw light on the question of the existence of a "coronary personality," an analysis of our material did not yield evidence pointing in this direction. Comparing their study with Dunbar's, Miles et al. raise the question as to the higher percentage of Jews in her study (59% compared with 35% in their group), suggesting that the features which she attributed to the "coronary personality" were really personality characteristics influenced by such cultural factors as family emphasis on education, ascent in the social scale, and material success.

The number of Jews (35%) in our coronary group was the same as in the Miles et al. study. Moreover, so far as the question of emotional factors preceding coronary occlusion is concerned, gradually mounting tension was just as common among Protestants and Catholics as among Jews. There were nine Protestants with gradually mounting tension (60% of the Protestant group) four Catholics (66% of the Catholic group), and eight Jews (57% of the Jewish group).

Iatrogenic Factor.—One of the most important and most difficult subjects in clinical medicine is the problem of anxiety and the heart. Many of the complicated problems that arise after coronary occlusion are of emotional origin and can only be understood when approached from that standpoint. Unfortunately the iatrogenic factor often adds to the problem by too much caution regarding physical exertion and inadequate attention to emotional factors. Many of the difficulties undoubtedly arise from the abuse of bed rest and precautions regarding activity and work. An anxious person with the symptoms of cardiac neurosis but with a normal heart can often be reassured and told to go about his business; an anxious person with a diseased heart cannot; but when he is told to rest and surrounded with other precautions he often becomes an invalid, more from the fear of heart disease than from the actual disease. Moreover, it seems to us that tensions of emotional origin can be as burdensome to the cardiovascular system as effort of physical origin, so that for both reasons one has to try to reduce anxiety in order to make such patients useful citizens again, within the capacity of their cardiovascular systems. Now and again such patients develop coronary occlusion or a cerebral vascular accident, and the physician may be criticized for overlooking or giving insufficient attention to the organic disease.

Strangely enough, cardiac neurosis prior to coronary occlusion seems to be uncommon from our studies, but when it does

happen it can be very hard on a medical reputation. The physician attempts to reassure the patient by excluding organic heart disease and blaming the symptoms on emotional factors. Then if the patient develops coronary occlusion, no matter how long afterward, neither he nor his family easily forgive the physician who had said that "the heart was normal."

This poses a very difficult question because the problems of psychosomatic relationships in cardiovascular disease may be very complicated and depend as much upon an analysis of personality structure as upon an evaluation of the cardiovascular disease. Therefore, one has to try to determine the degree of psychological impairment as carefully as the degree of organic heart damage, and judgment must be based on both. All of this means that the physician must understand the personality as well as the heart. Both have a structure that can be analyzed from a prognostic standpoint.

Summary

Some of the more important findings in a study of 43 patients with coronary occlusion from an emotional standpoint compared with a control group matched for age, sex, and race are presented. They suggest among the multiple factors having to do with coronary occlusion gradually mounting stress of emotional origin may be significant. It occurred in 49% of our cases, while no such evidence could be found in the control group. Acute emotional stress occurred in 16 (37%) of the coronary group and in only 4 (9%) of the control group. Evidences for gradually mounting tension will frequently be denied by the patient but suggested by a member of the family, often the spouse. Physicians must be trained in psychodynamics to obtain such information.

Among the unconscious mental factors that play a role in the gradually mounting tension is one we call the anniversary reaction, which is an unconscious association often based on a hostile identification with a dead parent. Evidence for this reaction was found in four of our coronary cases and probably existed in five others, whereas there were no such instances in the control group.

Problems of diminishing potency are frequent among the evidences of gradually mounting tension and in themselves seem capable of adding to the source of tension. Sexual problems antedating the occlusion were present in 21 (49%) of our coronary group, as compared with 10 (23%) in the control series.

Reaction to illness is determined by the personality structure of the patient. Most significant among these reactions is the one of denial in which the patient behaves as though he were not seriously ill, thus adding to the problems of medical care. On the other hand, regression, which leads to preoccupation with the illness and psychological invalidism, and mental depression, which may carry the threat of suicide, are also important reactions to coronary occlusion.

To neglect the study of emotional factors in coronary occlusion is to leave out of consideration an essential part of the clinical picture which may enter into the cause and certainly enters into the treatment of the disorder.

269 S. 19th St. (3).

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Treatment in Internal Medicine

The Treatment of Ulcerative Colitis

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Introduction

Ulcerative colitis is an acute and chronic disease of the colon and rectum, characterized clinically by bloody diarrhea, cramping abdominal pain, malaise, anorexia, fever, and weight loss.[1,2] Proctoscopic examination of the rectum and sigmoid reveals, in approximately 95% of cases, diffuse inflammation, with edema, granularity, ulceration, and friability of the mucosa and sanguinopurulent exudation. Roentgen study demonstrates loss of normal haustration of the colon, decreased distensibility, narrowing and ulceration of the bowel, and pseudopolypoid changes in the mucosa. The entire colon and rectum appear involved roentgenologically in approximately 50% of cases; in perhaps 10% the x-ray appearance is normal, presumably owing to limitation of the process to the mucosa; in the remaining 40% varying portions of the bowel are diseased. The adjacent terminal ileum also is affected in 10% to 15% of patients.[3] Ileocolitis involves chiefly the distal portion of the ileum, the cecum, and the ascending colon.

Ulcerative colitis most often affects young adults between the ages of 20 and 40 years, although no age group is exempt. The sex distribution is approximately equal, females predominating slightly. The incidence of ulcerative colitis is difficult to estimate. The reports in the medical literature probably represent chiefly the more severely ill patients observed at larger medical centers. The number of mild, unrecognized cases, not examined by proctoscopy and barium enema, is unknown, but undoubtedly is considerable. While the individual physician may encounter relatively few cases, the total incidence of the disease is higher than is appreciated generally.

The cause and pathogenesis of ulcerative colitis are not known. The disease has been attributed to infection with bacterial or viral agents, enzymatic and nutritional deficiencies, disorders of the basement membrane of the connective tissue of the colon and rectum, hypersensitivity or allergy to food or bacteria, the destructive action of proteolytic enzymes, and psychogenic and neurogenic mechanisms; none of these concepts has been established conclusively.

The course is characterized by a pronounced tendency to exacerbations and remissions. Recurrences are more likely at the time of upper respiratory infections and other intercurrent illnesses, physical fatigue, emotional tension, dietary indiscretions and, in women, at the menses. There are many complications. In the colon they include hemorrhage, giant ulceration, perforation, peritonitis, fistula formation, abscess, stricture, partial obstruction, polyps, and carcinoma, as well as electrolyte depletion and impaired absorption of fat from the small intestine. Systemic complications include vitamin deficiencies, anemia, hypoproteinemia, rheumatoid arthritis, vascular thromboses, iritis, erythema nodosum, pyoderma gangrenosum, hepatitis, fatty infiltration and cirrhosis of the liver, pancreatitis, glomerulitis, nephritis, and depletion of the

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adrenal glands. Immunological disturbances may occur, characterized clinically by drug sensitivity, severe reactions to blood transfusion, hemolytic anemia, and alterations in the plasma proteins.

In the absence of an established cause, there is no specific therapy. The treatment of ulcerative colitis is symptomatic, comprehensive, adapted to the individual patient, and prolonged, for months, years, and perhaps for life. The immediate objectives are rest, both physical and emotional, decrease in the hyperactivity of the colon, prevention or elimination of infection, restoration of nutrition, and healing of the colitis. Medical management, in our experience, is indicated in approximately 85% of cases.

The results of therapy are influenced by the severity of the illness prior to treatment,[4,5] the presence and type of complications, duration of the period of observation,[6] and the critical attitude of the observers. The problem of ulcerative colitis in the past is emphasized in a study of 2000 patients observed between 1918 and 1937[9]; only 56% were alive at the end of this period, in contrast to the expected survival rate of 83% for the general population. In another series, one-third of patients had died within five years.[10] The current record is better, though far from satisfactory. The decrease in mortality rate of ulcerative colitis from 50% to 5% over the past 50 years, despite lack of knowledge of etiology and specific treatment, emphasizes the progress accomplished. Nevertheless, ulcerative colitis continues to present a most difficult and perplexing therapeutic problem. The prolonged invalidism, frequent and lengthy hospitalizations, unpredictable recurrences, and many complications impose overwhelming medical, economic, and social problems, not recognized generally and fully appreciated only by the patient, the family, and the attending physician.

Diet

Ulcerative colitis is not caused by food sensitivity, dietary irritation, or nutritional deficiency. Nevertheless, a diet avoiding mechanical and chemical irritants, such as fresh fruits and vegetables; fried and spicy foods; fruit juices; chocolate; carbonated, malt, and alcoholic beverages, and excessively cold or hot foods, relieves abdominal discomfort and diarrhea.[11] A strict low-residue diet often seems helpful in acutely ill patients. This consists of the foods shown in Table 1. This menu contains only 1200 Cal., 130 gm. of carbohydrate, 40 gm. of protein, and 60 gm. of fat; it is inadequate in vitamins B and C; hence, it is prescribed only for several days. A bland, low residue, nonlaxative diet, without fruits and vegetables, is prescribed initially in the majority of cases (Table 2).

This menu occasionally is supplemented by feedings of milk, containing powdered foods rich in protein and carbohydrates, to increase the protein and caloric intake. Additions to the ulcerative colitis diet, prescribed when the feces are regularly well formed and do not contain blood, are shown in Table 3.

A more liberal intake of food is permitted in those persons who have maintained satisfactory health for long periods. The clinical improvement ascribed to the removal of "allergic" foods, such as fruit, bran cereals, and milk, seems attributable to the avoidance of irritating, high-residue foods.[12] Milk in large amounts may increase the

TABLE 1.—*Low-Residue Menu*

Breakfast	Lunch	Supper
Farina or Cream of Wheat	Clear broth	Poached egg on toast
Warm milk	Crisp toast	Butter
Melba or twice-baked toast	Boiled rice	Warm milk
Butter	Warm milk	Custard
Soft-boiled egg	Jello	Tea
Tea	Tea	

TABLE 2.—*Typical Low-Residue Non-laxative Diet (Without Fruits or Vegetables)*

Cereals	Farina, rice, Cream of Wheat, macaroni, noodles, spaghetti, vermicelli (no bran or whole-grain cereals)
Cheese	Cream, cottage, American, Swiss
Breads	White bread, toast, Melba toast, soda crackers, bread sticks, milk toast (no bran, whole wheat, or rye bread)
Eggs	Soft-cooked, soft-scrambled, soft omelet, soft-baked, poached, hard-cooked, creamed
Beverages	Lukewarm or warm milk, weak tea, weak coffee (no buttermilk, Ovaltine, or uncooked eggnogs)
Soups	Consomme, strained cream of rice, strained cream of potato
Meats and fish	Beef (boiled, broiled, or roasted) steak, hamburger, meat loaf; lamb; veal; scraped beef; creamed or sliced chicken; creamed salmon; tuna fish; boiled or broiled whitefish
Desserts	Rice, vanilla custard, plain bread, cornstarch pudding, plain Spanish or Bavarian cream, snow pudding, plain jello, plain cottage pudding with or without custard sauce
Cakes	Angel cake, icebox cake, sponge cake, plain cakes, arrowroot cookies

Representative Menu

Breakfast	Lunch	Supper
Cream of Wheat	Chicken broth	Consomme
Poached egg	Beef	Broiled whitefish
White toast with butter	Escalloped rice	Toast with cream cheese
Weak coffee	White bread with butter	Vanilla custard
Cream, sugar	Jello	Plain cake
	Milk	Weak tea, sugar

abdominal discomfort, flatulence, and diarrhea; however, many patients are able to take small or moderate quantities without difficulty.[13] There is considerable difference of opinion concerning the usefulness of diets in ulcerative colitis,[14-16] chiefly because of nutritional and psychiatric considerations. Nevertheless, in our experience, avoidance of irritants in the food is very useful in relieving the abdominal discomfort and diarrhea. For psychological reasons, restrictions in food intake are not as strict or as prolonged in children with ulcerative colitis. In adults, also, the diet should be adjusted to individual requirements; nutritional needs should not be sacrificed in the interest of a rigid low-residue program; in most instances both objectives are possible.

An adequate intake of protein and calories is important in the correction or prevention of nutritional depletion and hypoproteinemia resulting from the decreased intake of food, accelerated tissue catabolism, gastrointestinal bleeding, and the excessive loss of nitrogen in the feces. A diet containing 2500 to 3500 Cal., with 120 to 150 gm. of protein,[17] is desirable. A competent and interested dietitian is invaluable in providing palatable meals and in persuading patients to eat sufficient quantities of food. The usefulness of "medical ileostomy," including oral administration of a mixture of hydrolyzed protein and Dextri-Maltose, and constant suction of the distal small bowel probably is attributable chiefly to the nutritional advantages of this program [18-20]; however, we have rarely found it necessary to utilize this procedure. Tube feedings of food products rich in protein and carbohydrate may be helpful in selected instances, though they are definitely less preferable than good quality whole foods. Various mixtures are available; one combination includes three-fourths of a quart each of milk and cream, 180 gm. Gevral (vitamin, mineral, and protein supplement), 360 gm. of powdered skimmed milk, 330 gm. of sugar, and 3½ oz. of lean meat are homogenized and diluted with water to a volume of 2000 cc.; the preparation is introduced by a pump through an indwelling plastic gastric catheter at a rate of 80 cc. per hour; this mixture provides 5000 Cal. and more than 250 gm. of protein; however, it often increases bowel motility and aggravates the diarrhea. Complete nutritional repletion

TABLE 3.—*Additions to Ulcerative Colitis Diet*

Cooked or canned vegetables	Asparagus, carrots, peas, string beans, spinach, pureed tomato
Cooked or canned fruits	Apple sauce, peaches, apricots, pears, pureed prunes
Potato	Baked, mashed, whiped or riced

ordinarily cannot be accomplished in a short time; several months or more should be allowed for this purpose, if necessary.

Solutions of 5% dextrose and isotonic saline, containing appropriate amounts of potassium salts, may be required intravenously to restore electrolyte and fluid balance. Blood transfusions, 500 to 1000 ml. in amount, are valuable in correcting anemia and hypoproteinemia. Because of frequent transfusion reactions, the blood typing and cross matching should include the minor blood groups; the blood is administered slowly at room temperature; the addition of 20 mg. of chlorpheniramine (Chlor-Trimeton), or a similar antihistaminic preparation, may reduce the frequency and severity of reactions. Plasma, 500 ml. stored at room temperature, or salt-poor human albumin, 50 gm., also are helpful in correcting hypoproteinemia; the amount to be administered depends upon the severity of the protein depletion. Iron preparations, including Proferrin (colloidal iron saccharate) and Imferon (iron-dextran complex), given intravenously or intramuscularly in total doses of 0.5 to 2.0 gm. in divided amounts, are valuable in the treatment of the iron-deficiency anemia so often present. Iron by mouth is highly irritating to the bowel in patients with ulcerative colitis, aggravating the abdominal discomfort and diarrhea, and hence should not be prescribed. Multivitamins, added to the intravenous fluids or taken orally, also are useful; however, excessive quantities are irritating to the gastrointestinal tract and should be avoided; there is no evidence, furthermore, that large amounts of vitamins are necessary.

Rest and Sedation

Emotional tension and physical fatigue are important factors in the recurrence and chronicity of ulcerative colitis. Adequate rest and sleep, pleasant recreation, and decreased responsibility help diminish the hyperactivity of the colon. Complete bed rest is essential during the active stages of the disease. Increasing activity is permitted as the fever, abdominal distress, and diarrhea subside. The amount of physical and emotional rest adequate for a given patient should be determined individually. Prolonged inactivity, in the absence of active disease, is harmful, not only emotionally but also physiologically; children especially seem to thrive better with activity than with confinement to bed. A pleasant, interesting occupation, with a minimum of nervous tension and avoiding excessive physical activity, contributes greatly to the rehabilitation of the patient.

Sedatives promote relaxation and sleep. Phenobarbital, 30 mg., combined with extract of belladonna, 7.5 mg., four times daily, or triple bromides, 1.0 gm. four times daily, are prescribed frequently. Chloral hydrate, 1.0 gm.; secobarbital (Seconal), 100 mg.; pentobarbital (Nembutal), 100 mg.; Tuinal (a combination of equal proportions of secobarbital and amobarbital), 100 mg., or glutethimide (Doriden), 0.5 gm., among many compounds, may be given at bed time to facilitate sleep.

Antispasmodic and anticholinergic compounds diminish hyperactivity and spasm of the large bowel and rectum. Though their effects are highly variable, not infrequently they reduce the urgency to defecate and the number of bowel movements. The more popular drugs include atropine sulfate, 1/100 grain (0.65 mg.) subcutaneously or by mouth; belladonna tincture, 10 to 15 drops; diphemanil (Prantal), 100 mg.; mepiperphenidol (Darstine) 100 mg.; penthienate (Monodral), 5 mg.; propantheline (Pro-Banthine), 15 mg., and methscopolamine (Pamine), 2.5 mg., taken four times daily before meals and at bedtime. In an effort to diminish the hyperactive gastrocolic reflex, these compounds often are prescribed in larger amounts at bedtime and in the morning before breakfast. Since individual responses and tolerances for these drugs vary considerably, it may be

necessary to prescribe several compounds to determine the most effective preparation for the individual case. In debilitated patients, the more potent anticholinergic drugs may inhibit intestinal motility so profoundly as to produce atony and complete suppression of peristalsis; bowel motility usually is regained within 48 to 72 hours after discontinuance of the medication.

Codeine sulfate (30 or 60 mg. every four hours), deodorized opium tincture (10 drops four times daily) or meperidine (50 to 100 mg. intramuscularly every four to six hours) may be prescribed for rectal tenesmus and severe abdominal cramps and to decrease the gastrocolic hyperactivity. These compounds are especially valuable during acute stages of the disease. They also may be useful during the recovery phase, permitting patients to increase their activity without the embarrassing possibility of precipitous, uncontrolled bowel movements; however, their use should be limited, to avoid the possibility of addiction.

The so-called "tranquilizing" drugs—reserpine, 0.25 mg. four times daily; meprobamate (Miltown or Equanil), 400 mg. four times daily; promazine (Sparine), 25 mg. four times daily, and hydroxyzine (Atarax), 25 mg. four times daily—also may promote rest and relaxation, although their usefulness in ulcerative colitis is not yet established.[21,22] Chlorpromazine, 25 to 50 mg. four times daily, may be very helpful in emotionally disturbed, agitated patients and in the management of "steroid psychosis."[23] Reserpine probably is not desirable in ulcerative colitis because of its tendency to increase bowel activity, in some patients at least.

Psychotherapy

The role of psychogenic factors in the pathogenesis of ulcerative colitis is neither clear nor fully accepted.[24-27] There are numerous unsolved problems, including the question of psychosomatic versus somatopsychic relationships, the specificity of the emotional disorder attributed to ulcerative colitis, the objectivity of the psychiatric observations, and the mechanism of action of psychogenic disturbances upon the colon.[28-30] Nevertheless, emotional disorders often are associated with the onset or recurrences of the disease.[31-33] The incidence of psychiatric problems among persons with ulcerative colitis is very high. Patients often are emotionally disturbed, dependent, immature, self-depreciating, and hostile[34]; they seem to be unusually fragile and hyperreactive, even to ordinary events of daily life.

Thorough understanding of the patient's emotional difficulties and skillful attention to these problems, therefore, are essential in the effective management of the disease. In some cases, supportive psychotherapy by the internist or psychiatrist may be very helpful.[15,16] Formal psychiatric management is not indicated in most patients. In fact, "uncovering" psychotherapy may be extremely hazardous in severely ill cases,[35] for patients then are unable to cope with the problems; the resulting conflict may precipitate a serious and even fatal recurrence. Emphasis only upon the emotional aspects of ulcerative colitis is dangerous because unrecognized or inadequately treated organic problems may lead to serious complications. The internist and psychiatrist should cooperate closely, therefore, if joint management is undertaken. Psychoanalysis, in our experience, has not produced lasting benefit in the small number of patients so treated; the nature of this technique limits its application to a few highly selected cases.

The most helpful psychotherapeutic approach appears to be that of the interested, intelligent, and sympathetic family physician, constantly providing support, reassurance, and encouragement in frequent visits with the patient. The discussions should include anything of interest or importance to the patient, sports, politics, literature, art, music, or other topics, no

matter how trivial, avoiding the details of bowel function and related symptoms. The enthusiastic and kindly approach of the physician, manifesting special interest in the patient and in his or her problems, is very effective in generating confidence and hope for ultimate recovery. The patient's family and home environment also requires careful attention. Not infrequently, psychotherapy must be directed to a parent, husband, or wife, and the success or failure of treatment may be determined by the ability to influence the family and the environment to the benefit of the patient. Supportive psychotherapy also is very necessary in patients requiring surgical treatment, for the adjustment to colectomy and ileostomy may be extremely difficult.

There is no conclusive evidence of a fundamental, permanent disappearance of the emotional defects of most patients following successful medical treatment. Nevertheless, occasionally there appears to be a striking change in personality, at least superficially, characterized by a more mature orientation to life and by the development of poise and confidence. Dependence upon the physician gradually lessens as the patient eventually is restored to an adequate, albeit imperfect, emotional adjustment.

Unfortunately, because of the considerable time required, the high cost of the usual psychotherapeutic program, and the insufficiency of hospital beds for long-term care, this approach, as useful as it may be, is limited to very few patients. Unlimited patience and equanimity are required. The physician who lacks the interest to deal with the emotional and medical problems on a long-term basis should not undertake the management of the patient and his disease.

Sulfonamides-Antibiotics

Although no bacterial or viral agent has been identified as the cause of ulcerative colitis, the fever, the "toxemia," the purulent rectal discharge, the proctoscopic appearance, and the various complications, especially abscess and fistula formation and pericolitis, indicate an inflammatory disease. No consistent correlation has been demonstrated between the identifiable bacterial flora of the feces and the clinical course.[36,37] However, symptomatic improvement occasionally is related chronologically to suppression of hemolytic coliform, Streptococcus or Staphylococcus bacteria in the feces; the clinical response may continue during prolonged therapy, despite apparent return of the bacterial flora to original conditions.[38]

Sulfonamides are prescribed to control or prevent secondary bacterial infection of the bowel and in the hope of eradicating as yet unidentified bacterial or viral agents. The compounds administered most often are sulfaguanidine, 8.0 gm. daily; phthalylsulfathiazole (Sulfathalidine), 4.0-6.0 gm.; sulfadiazine, 2.0-4.0 gm., and salicylazosulfapyridine (Azulfidine), 4.0-8.0 gm. daily. No single sulfonamide appears to surpass all others. Although salicylazosulfapyridine has been recommended enthusiastically,[39-42] our experience with this compound has not been especially striking. Frequently, after initial improvement, the beneficial effect wanes, presumably because of overgrowth of less susceptible bacteria. A change in the sulfonamide preparation may be followed by a renewed clinical response. Many patients have been maintained on continuous sulfonamide therapy for long periods by this technique of alternating sulfonamide administration.

The use of antibiotics occasionally may be accompanied by a clinical response similar to that observed with sulfonamides.[46-49] The combination of penicillin, 1,200,000 units, and streptomycin, 1.0 gm., intramuscularly daily has been effective, in our experience, in the management of systemic infection or periocolitis complicating ulcerative colitis; this dosage is maintained for five to seven days. The streptomycin then is discontinued and replaced by a sulfonamide orally until the infection subsides.

Sulfonamides also are prescribed routinely as a prophylactic measure during the administration of corticotropin (ACTH) and the adrenal steroids; the incidence of complicating infections and perforation of the bowel seems to be reduced significantly as a result.

The adverse side-effects of antibacterial medication—nausea, vomiting, excessive flatulence, skin rashes, leukopenia, and renal damage—constitute an occasionally serious problem. The temporary antibacterial action, the development of bacterial resistance, and the inconstant clinical response are more important limitations to sulfonamide therapy. Nevertheless, we consider sulfonamides beneficial in reducing the incidence and hazards of purulent complications and also in contributing to the remissions of the disease.[50]

Corticotropin and Adrenal Steroids

Corticotropin and the adrenal steroids decrease the cellular and vascular responses to inflammation in ulcerative colitis as in other diseases; there is no evidence at present of a specific action upon the disease process. Their use in 1950 was prompted by the occurrence of rheumatoid arthritis, iritis, and erythema nodosum in ulcerative colitis and by the beneficial effects of the adrenal hormones observed in these diseases.[51,52] Subsequent evaluation of the steroids has ranged from cautious endorsement to strong disapproval.[53,54] Many studies have demonstrated a striking, at times dramatic, clinical response in ulcerative colitis.[55-57] The improvement is similar to that accompanying conventional therapy, but it occurs more frequently and more rapidly.[58-60] The response is characterized by prompt disappearance of fever, toxemia, diarrhea, and abdominal discomfort; increased appetite and sense of well-being, and by gradual subsidence of the proctoscopic changes.[61] The sedimentation rate, when elevated, returns to normal; excessive loss of nitrogen in the feces subsides. Serial rectal biopsies demonstrate histological evidence of healing, with disappearance of inflammatory cells, although the return to normal usually is not complete.[62] Lack of a significant clinical response to steroids, including corticotropin intravenously, during a period of 10 to 14 days signifies that hormonal therapy probably will not be adequate in a given case.

Corticotropin and the adrenal steroids are potent agents, causing profound biologic and biochemical changes and numerous complications. The most frequent problems are those resulting from the physiological properties of the hormones: Cushing-like changes characterized by edema, moon facies, hirsutism, acne, "buffalo-type" obesity, hypertension, hypokalemia, and hypochloremic alkalosis. Hyperglycemia and glycosuria develop less frequently; diabetic patients may require an increase in insulin, temporarily. Severe infections have been infrequent in our experience.[63] Emotional disturbances occur in 5% to 10% of cases and consist chiefly of manic and delusional states, with a risk of suicide in some instances. The development of severe mental disturbances during steroid therapy necessitates rapid decrease in dosage and discontinuance of the medication; this usually can be accomplished within 72 to 96 hours. Increased sedation and restraints may be necessary. Chlorpromazine, 100 to 200 mg. daily, may be especially valuable in controlling the agitation. The development of a toxic psychosis in patients with ulcerative colitis often is accompanied by a dramatic improvement in the colitis, permitting rapid diminution and discontinuance of the steroids; the medication may be resumed later, if necessary.

Careful observation of the patient, preferably in the hospital and frequent determinations of the serum electrolytes, erythrocyte and leukocyte counts, blood sugar, and urine analysis facilitate early recognition of the various complications and prompt appropriate treatment. Potassium deficits

are corrected by the intravenous administration of 40 to 160 mEq. of potasisum chloride daily; potassium salts orally are irritating to the bowel in patients with ulcerative colitis and are not prescribed routinely. The routine administration of potassium salts has not been necessary, in our experience. Indeed, patients may tolerate pronounced alterations in serum electrolytes with comparatively few symptoms. Most of the complications caused by corticotropin and adrenal steroids can be managed by reductions in dosage, change of preparation, and moderate restriction of salt intake.

The gastrointestinal complications—perforation of the colon, giant ulceration of the bowel, massive hemorrhage and reactivation of peptic ulcer[64-67]—attributed to steroids, have been encountered only rarely in our experience. These problems complicated the course of ulcerative colitis long before the advent of steroids.[1,68,69] There is no satisfactory evidence that steroid therapy has increased their incidence significantly. Peptic ulcer has developed in only 1 of 180 patients with ulcerative colitis receiving large quantities of steroids for long periods of time; in that case healing occurred promptly after the administration of antacids, despite continued steroid therapy. Adrenal hemorrhage, intractable shock after operation, and activation of latent tuberculosis, though reported in the literature, have not been observed.[70]

The indications for steroid therapy in ulcerative colitis are (1) recurrent severe disease despite careful and comprehensive medical management in the hospital; (2) the presence of complications, such as rheumatoid arthritis, iritis, and erythema nodosum, and (3) acute fulminating ulcerative colitis. Contraindications to the adrenal hormones in ulcerative colitis include the presence of purulent complications, such as abscess and fistula formation, perforation, and peritonitis. Steroids are not contraindicated in the presence of pericolitis and peritoneal irritation; indeed, hormonal therapy under such circumstances may be very helpful in controlling further extension of the disease process. A past history of tuberculosis or peptic ulcer does not exclude the use of steroids when the indications are otherwise adequate; isoniazid, 300 mg. daily, with or without aminosalicylic acid, has been prescribed, together with the hormonal therapy, in a few patients with a past history of extensive pulmonary tuberculosis. Antacids are not prescribed routinely.

Corticotropin is the most potent of the adrenal compounds available at present. It is administered usually as the aqueous preparation, initially in doses of 30 units every six hours intramuscularly, for a total dose of 120 units in 24 hours; 160 or 200 units may be necessary in selected cases. In patients not responding to corticotropin intramuscularly, it may be given intravenously by slow drip, 20 units in a solution of 5% dextrose in water during a 12-hour period, twice in 24 hours. Repository corticotropin injection is administered chiefly as maintenance therapy, in single daily doses of 40 to 80 units daily; it has not been as effective as anticipated originally. Hydrocortisone also may be administered intravenously in quantities of 25 or 50 mg. every 12 hours. Hydrocortisone hemisuccinate may be injected intramuscularly in doses of 50 or 100 mg. every four to six hours. Long-acting corticotropin zinc, 40 to 80 units intramuscularly, apparently has been useful in some cases; our experience with this preparation has been limited. The orally administered steroids in decreasing order of potency are hydrocortisone (200 mg. daily), prednisone (40-80 mg.), prednisolone (40-80 mg.), and cortisone (300 mg.).[64] Hydrocortisone also may be instilled locally into the rectum as the ointment or as a retention enema (20 or 30 mg. in several ounces of isotonic saline).

Initial therapy frequently is with aqueous corticotropin intramuscularly. As clinical recovery progresses, the dose is reduced

gradually, depending upon the course of the individual patient, perhaps by decrements of 10 units every five to seven days. When the intake is diminished to 30 or 40 units daily, the corticotropin may be replaced by hydrocortisone or prednisone orally; the transition is completed over a period of several days, on the arbitrary basis of one unit of corticotropin equivalent to 1 mg. prednisone or to 2 mg. hydrocortisone. Steroid therapy is maintained, on the average, for a minimum of several months. Prolonged treatment for one to three years has controlled the disease effectively in numerous patients. Maintenance dosage schedules are on the order of corticotropin, 20 units; hydrocortisone, 40 to 80 mg., and prednisone, 15 to 30 mg. daily. Recurrences during steroid therapy usually are attributable to intercurrent illnesses, especially upper respiratory infections, emotional disturbances, dietary indiscretions, and premature reductions in dosage. The discontinuance of these compounds often is quite difficult and must be accomplished very gradually; too rapid reductions in steroid dosage may be followed by recurrence of symptoms. Endogenous adrenal stimulation with corticotropin often is recommended after the prolonged administration of hydrocortisone, cortisone, or prednisone; however, an adequate adrenal response may not develop for one or two weeks of corticotropin therapy. In our experience with the long-term use of the adrenal steroids, no untoward effects have been observed attributable to our failure to employ periodic adrenocortical stimulation.

Steroids are discontinued ideally under the following conditions: no proctoscopic evidence of the disease, normal bowel function, feces negative for blood and pus, normal white blood cell count and sedimentation rate, and correction of anemia; x-ray evidence of healing is desirable, but it is not to be expected except after long periods of sustained improvement.[72] All other methods of therapy—rest, sedation, diet, supportive psychotherapy, and nutritional care—must be continued during the administration of corticotropin and the adrenal steroids. Sulfonamides are prescribed routinely in all cases and should be continued at least for the duration of the steroid treatment.

Corticotropin and adrenal steroids do not cure ulcerative colitis. They do not replace established methods of treatment; nevertheless, they are useful adjuncts to standard therapy.[73] Eighty-five per cent of patients can be expected to respond initially. Recurrences develop frequently when the quantity of steroid is reduced or the medication is discontinued; renewed treatment tends to be less effective than the initial course, but, nevertheless, controls the symptoms in most cases. Corticotropin and the adrenal steroids thus seem to act as "therapeutic bridges" during periods of active disease, allowing more effective application of other methods of treatment. Prolonged adrenal hormonal therapy may be helpful in the prevention of recurrences and thereby obviate the necessity for disagreeable surgical procedures.

Miscellaneous Materials.—There is no satisfactory evidence that the following materials—amebicidal drugs, antilysozyme preparations, antidysentery serum, bacteriophage, vaccines of various types, antihistaminics, antithyroid drugs, medicated enemas, ascorbic acid, cobra venom, parathyroid hormone, animal-tissue extracts, isoniazid, apples, hydrochloric acid, insulin, Kaomagma (aluminum hydroxide gel and kaolin), liver extract, psyllium hydrophilic mucilloid (Metamucil), mucin, rutin, and salicylates—are of therapeutic value in ulcerative colitis. Indeed, these preparations often increase the abdominal discomfort and diarrhea.

Surgery

The frequent recurrences of ulcerative colitis, numerous complications, improvements in surgical techniques,[74,75] and the lowered mortality rates have increased interest in the surgical management of the

disease. The incidence of surgical treatment in ulcerative colitis varies widely; 5% at the Mayo Clinic,[76] 9% at the University of Chicago Medical Center, 20% in New York[77] and California,[78] and 47% in Boston.[79]

The indications for surgery in ulcerative colitis are extensive abscess or fistula formation, stricture with obstruction, perforation, extensive polyposis, recurring massive hemorrhage and carcinoma strongly suspected or established, rheumatoid arthritis, portal cirrhosis of the liver, severe anemia, iritis and pyoderma gangrenosum unresponsive to medical treatment, perhaps severe growth failure in children, and, in the absence of complications, lack of response of the disease to comprehensive and prolonged medical treatment in the hospital[80-82]; this last indication is difficult to formulate and will be determined largely by the orientation of the physician to medical or surgical management. The decision should not be made hastily; nor should it be determined solely by economic reasons. Surgeons emphasize as additional indications for operative intervention chronic invalidism[83,84] and ulcerative colitis exceeding 10 years in duration, because of the increasing possibility of carcinoma.[85] Evaluation of chronic invalidism in the individual patient with a disease characterized by unexplained remissions and exacerbations is difficult. We have observed satisfactory improvement in numerous patients advised previously to undergo surgery for this reason. The question of potential neoplasia in ulcerative colitis also is difficult to deal with clinically. Colectomy and ileostomy in a child, young man, or young woman because the disease has exceeded 10 years, despite satisfactory or excellent general health, seems unnecessarily radical. The situation may be analogous to prophylactic gastrectomy in all patients with pernicious anemia because of the high incidence of gastric carcinoma in such cases. There is no completely satisfactory solution to the problem. However, annual study of the patient would seem to be a more satisfactory practical approach at the present time.

The operative treatment of choice is ileostomy and colectomy in one or two stages.[86] Ileostomy alone does not cure ulcerative colitis, nor is healing after this procedure sufficiently complete to permit restoration of normal bowel continuity, except in rare cases. Abdominoperineal resection is necessary when the rectum is irreversibly diseased and is the source of recurrent bleeding and infection. In segmental colitis of the cecum or the ascending and transverse colon not responding to adequate medical treatment the operative procedure usually is limited resection of the diseased bowel, with restoration of normal continuity. Subtotal resection of the colon with anastomosis of the ileum to the remaining rectal segment, so-called "rectal ileostomy," also has been performed in selected cases with little or no involvement of the rectum. Vagotomy and pelvic autonomic neurectomy have not been accepted generally; appendicostomy and cecostomy have been discarded.[89] Prefrontal lobotomy at present is an experimental procedure; until more conclusive favorable evidence is available, its use is not recommended.[88,89]

Surgical treatment may be extremely effective and, at times, life-saving. Occasionally it is the only procedure for restoring patients from a state of chronic invalidism to a useful life. Long-term surgical results indicate that 75% to 85% of cases are in good health and employed.[90-92] However, despite the lowered mortality rate, the operative results are not entirely satisfactory. Indeed, the morbidity and chronic invalidism may be increased after surgical intervention. In the Mayo Clinic series, only 14% of patients were free of complications at the end of one year.[93] Although medical treatment has produced better results in the past few years, surgical morbidity has remained the same.[67] The most frequent complications are bleeding, prolapse, retraction, fistula formation, perforation and

stenosis of the ileostomy, excoriation of the skin, inability to maintain an ileostomy bag in proper place, intestinal obstruction, extension of the disease into the ileum (or involvement of the small bowel unrecognized at time of operation), recurrent electrolyte and fluid depletion, and difficulties in the emotional adjustment of the patient to the ileostomy;[77-79,92,93] the latter problem is especially serious in the child or young adult.[94-96] Failure to remove the severely diseased rectum may result in repeated rectal hemorrhages or recurrent infections. X-rays of the small bowel and careful studies of fat absorption are necessary to avoid especially hazardous operations on diseased ileum. Prolonged steroid therapy, inadequate intake of food, and excessive loss of nitrogen may produce serious nutritional depletion, delaying wound healing and promoting infections. On the other hand, careful administration of steroids, adequate nutritional care, and prophylactic chemotherapy permit almost all patients to negotiate colectomy and ileostomy when necessary without serious difficulty. In patients receiving corticotropin or the adrenal steroids who are to undergo surgery, large amounts of cortisone or hydrocortisone prior to and during the postoperative period are necessary intramuscularly to maintain adequate adrenal function during and immediately after the operative procedure. Our experience with ileostomy and colectomy has been extremely variable. While the rehabilitation of some patients has been almost dramatic, many other patients have continued to experience an endless succession of problems requiring frequent hospitalizations; the mortality rate subsequently has not been inconsequential. The most careful medical management, therefore, is necessary before surgery is recommended. Operative treatment should be undertaken only after careful evaluation of all details.

Summary

Medical treatment is satisfactory in approximately 85% of patients with ulcerative colitis. Therapy consists of physical and emotional rest, sedatives, antispasmodics, and, occasionally, tranquilizing drugs; a low-residue, nutritious diet; vitamins; correction of anemia and hypoproteinemia; maintenance of electrolyte and fluid balance, sulfonamides, and supportive superficial psychotherapy by the attending physician. Corticotropin and the adrenal steroids, especially hydrocortisone and prednisone, though not curative, are useful adjuncts, serving as "therapeutic bridges" and permitting more effective application of other methods of treatment. Complications, especially those related to the physiological properties of the hormones, are numerous, but they can be managed adequately by constant vigilance and by repeated laboratory studies. Remissions of the disease occur initially in approximately 85% of patients receiving adequate quantities of steroids. Recurrences are frequent; further treatment may not be as successful as the original program, but, nevertheless, it usually is worth while. Prolonged therapy helps to maintain some patients in satisfactory health for long periods of time.

Surgical treatment is indicated for impending or actual perforation of the bowel, extensive perirectal abscess and fistula formation, stricture with obstruction, recurrent exsanguinating hemorrhages, polyposis, and carcinoma. Operation may become necessary in the presence of severe rheumatoid arthritis, certain infections (especially iritis and iridocyclitis) unresponsive to medical management, and perhaps in occasional children with severe growth failure. Other potential indications are acute fulminating colitis and severe colitis without complications not responding to careful medical treatment in the hospital. Hemorrhoids and localized fistula formations are treated conservatively. The operative procedure of choice is ileostomy and total colectomy in one or two stages. The Koenig-Rutzen bag is an effective contrivance for the ileostomy. Surgery may be life-saving and occasionally

the only method for restoring a chronic invalid to a relatively satisfactory life. However, it may be followed by numerous complications, including bleeding, prolapse, stenosis, abscess, or fistula formation of the ileostomy; partial intestinal obstruction; ulcerative enteritis, and intractable electrolyte and fluid depletion. Failure to remove the extensively diseased rectum may be followed by recurrent infection and hemorrhage. Surgery should be undertaken only after careful medical treatment in the hospital. The decision for operation should not be based upon theoretical considerations or upon the frustration of the physician; nor should it be determined solely by lack of funds to provide for proper medical attention. Many patients will respond to continued comprehensive medical management. Occasionally there is striking reversibility of the condition of the diseased colon toward normal.

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Case Reports

Hepatolenticular Degeneration

Follow-Up Report of a Case Treated with Dimercaprol (BAL), Potassium Sulfide, and High-Protein Diet

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Since the first report of this case, in this journal (1953),[1] there has been considerable progress in the elucidation of copper metabolism in man[2] and the biochemical pathophysiology of Wilson's disease. The suggestion that the neurological manifestations of this condition are related to the positive copper balance, with alteration in structure and function of the brain secondary to copper deposition therein,[3] has been widely, though not universally,[4] accepted and is further supported by this report. Copper absorption from the gut is greatly increased.[5] Transport of most of the plasma copper, loosely bound to protein, in the absence of sufficient ceruloplasmin[6-8] allows deposition of copper in the tissues. Excretion through both liver and kidneys is reflected in the high values in the bile[9] and urine.[10] In the latter, it is supposed that the deposition of copper in kidney tissue precedes aminoaciduria,[11] and then these amino acids and peptides in turn chelate copper, accounting for elevated urinary values paralleling the aminoaciduria.[12]

Diagnosis is usually made on clinical grounds. Though diagnostically helpful, biochemical determinations of abnormalities are available only at research centers. Recently a rapid and simple estimation of serum oxidase activity has been devised.[13] This may soon become a very important laboratory aid in early diagnosis, as it is probably feasible to perform in the usual clinical laboratory.

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Treatment of patients with Wilson's disease consists of the administration of (1) chelating agents parenterally (dimercaprol,[14] edathamil calcium-disodium [Calcium-Disodium Versenate]) to promote excretion of copper; (2) copper-binding chemicals orally (potassium sulfide) to prevent absorption of copper from the alimentary tract, and (3) diet (low copper) with the aim of decreasing intake of copper, or diets (high protein, supplemental casein hydrolysate P. O. and/or I. V.) to enhance the urinary excretion. Various schedules of dimercaprol administration have been reported.[13,14] No previous account has been found of uninterrupted daily administration over many months. This feature of treatment and the marked improvement under treatment in a previously described case constitute the bases of this follow-up report. The method of Cartwright et al.[11,15] was used in planning treatment.

Report of Case

History.—A 32-year-old white man was found to have Wilson's disease in September, 1950, two and one-half years after the gradual onset at the age of 24 of tremor and personality changes.[1] Approximately six months prior to that hospitalization he experienced difficulty in walking, and his behavior deteriorated. A mild dementia appeared, with memory disturbance and moria. The month prior to admission, difficulties in swallowing and phonation were noted. The most prominent neurologic finding at that time was a slow, rhythmic, constant, wing-beating tremor which was aggravated by posture-holding and stopped by voluntary motion. Fine movements and skilled acts were performed poorly. His face was expressionless, and in walking he showed a wide-based stride. Behaviorly, the usual social restraints were in abeyance, and the patient was very irritating to all with whom he came in contact. During the

subsequent 18 months there was slight deterioration in the neurologic findings, with the appearance of a superimposed Parkinsonian type tremor in both hands.

He was then given 0.32 gm. of dimercaprol in six divided doses on one day. Ten days later he was given an eight-day course of 0.44 gm. per day divided into two doses. One month following this, improvement was noted in the tremor and behavior. The patient had refused further treatment at the time of the previous report.

We first saw the patient on Nov. 16, 1955, when he was transferred to the neurology service from the East Louisiana State Mental Hospital, where he had been committed. He had been bed-ridden for at least three months. Information received from the V. A. Hospital showed that the patient had received several further courses of treatment since the previous report, as seen in Table 1.

TABLE 1.—*Courses of Treatment*

Date		Dose Dimercaprol (1%) Cc. B.I.D.	Improvement	Comment
Started	Stopped			
6/30/53	7/6/53	2.2	—	Nausea, difficulty swallowing
7/9/53	7/23/53	2.2	+	
8/25/53	10/8/53	2.0 (twice weekly)	0	

After this last course the patient did not return to the V. A. Hospital, and there is no reliable information about him during this subsequent two-year period. It is known that he bruised his head frequently in stopping himself, as he was observed by one of us in passing on the street once during this interval. He was stooped forward at the hips, with arms straight down toward the ground and wrists flapping violently. His gait was propulsive and festinating as he went from one telephone pole or street lamp to the next, which he would contact with great impact, recoil, and then start again. A hematoma had been seen on the cheek at that time.

Examination.—Admission examination showed a chronically ill white man. Facial expression was mask-like, with retracted upper lip, giving an appearance of a sardonic smile. The eyes were widely open, and blinking was infrequent. There was a coarse nystagmus on conjugate gaze away from the primary position. Barely audible monosyllabic responses could be made with great difficulty. There was an inconstant tremor of the jaw. Swallowing a sip of fluid took as long as a minute, and solid food remained in the mouth. A cogwheel type of rigidity was present in the musculature of the extremities. Occasionally a coarse tremor could be seen in the right arm or leg at rest. There was great difficulty initiating voluntary movement in response to commands. Once started, however, the movement was accompanied by an intention tremor. This became especially violent as the hands approached the face. Placement of the finger-to-nose could not be attained. No sensory abnormalities were detected. The corneal Kayser-Fleischer rings were very deeply pigmented. Telangiectasia was marked over the thorax. The rounded edge of the liver was barely palpable.

Laboratory Data.—RBC, 6,500,000; WBC, 9600 (64 segmented cells, 33 lymphocytes, 2 monocytes, 1 basphile); urinalysis, normal; S. T. S., negative; B. U. N., 13.8 mg/100 cc.; serum protein, 6.9 gm/100 cc. (A/G, 4.4/2.5); thymol turbidity, 9.7; cephalin floculation, 1+; bilirubin, 0.79 mg/100 cc.; uric acid, 2.46 mg/100 cc.; BSP, 10.5% retention; CSF protein, 106 mg/100 cc. (normal for lab., CSF protein less than 51 mg.); gold curve, 3333221000. Dec. 20, 1955, EEG within normal limits.

Clinical Course.—Treatment was started with potassium sulfide, 20 mg. t. i. d., with meals; a high-protein diet (liquid, soft, then regular as improvement ensued) with supplementary feedings of amino acids, polypeptides, and eggnogs, malted milks, etc., and dimercaprol (BAL), 1.7 cc. (17 mg.) I. M. every 12 hours. On the fifth day there was increased difficulty swallowing, and the patient appeared more acutely ill. A single injection of 1.7 cc. of dimercaprol was given daily from then on. The improvement was as indicated in Table 2.

TABLE 2.—*Observations of Improvement During Treatment*

Date	Day of treatment	Observations
11/23/55	1	
11/27/55	5	Difficulty swallowing; improvement started from this day
12/9/55	17	Could smoke using both hands to bring cigarette to lips; less rigid; placed in chair
12/10/55	18	Jaw tremor gone; speech much clearer; vertical eye movements possible without nystagmus
12/15/55	23	No nystagmus in any direction; sat up by self; could close mouth
12/18/55	26	Walked with assistance; reported greater ease in swallowing
12/19/55	27	Able to go to lavatory with help
12/25/55	33	Walked 5 steps alone
12/27/55	35	Tremor noted to be markedly decreased by several observers
1/5/56	44	Fed himself (but very messy) first
1/15/56	54	Walked without assistance
2/27/56	97	Started trying to shave self (safety razor)
3/3/56	104	Able to shave and dress self completely; tremor elicited only on strong emotion or fatigue

After this initial three and a half month period under treatment, improvement was not so dramatic, yet it was clearly present (recorded cinematographically). His movements achieved much more grace, and his speech became more inflected and expressive. He was able to attend hospital dances, and he enjoyed popularity because of his performance to the tunes of faster tempo, though it is

suspected that this was less because of his agility than because of his uninhibited exhibitionism. His behavior became intolerable to hospital personnel because of constant sexual preoccupation and expression. He was discharged on May 18, 1956, one hundred eighty-four days after admission, to continue treatment at home. CSF protein on April 30, 1956, three weeks before discharge, though still higher than normal (less than 51 mg/100 cc.), had come down to 73 mg/100 cc., and the gold curve had become more flat: 211000000.

Comment

Two points are worthy of note in this case, dimercaprol injections were well tolerated in dosage given daily for over six months. A difficulty with dimercaprol administration is that, in usual doses, toxic reactions occur, and the drug must be discontinued. The aim of uninterrupted administration was to produce a continuous tendency toward negative copper balance. By itself, the dosage used was probably too small to have changed the sign of the balance. Though we have no clinical or laboratory controls, it is the opinion of several observers on the basis of their past clinical experience that the improvement was too dramatic to have been accounted for by the injections alone. The other factors in treatment were the potassium sulfide and the high-protein diet. It is assumed that these (especially the sulfide) played a major role in inducing and maintaining the improvement.

Though this report covers but a single case, it shows that striking remission of signs and symptoms took place. With the implication that this may be possible in other cases, and with the possibility that such treatment may be able to prevent the appearance of pathological neurologic manifestations, encouragement is given toward our attack on this disease. This is especially so since the report of a rapid, easy, diagnostic test; for the earlier the diagnosis, presumably, the more readily reversible or preventable the manifestations.

Summary

Dramatic improvement is seen in a far-advanced case of Wilson's disease treated with dimercaprol (BAL), potassium sulfide, and a high-protein diet. No toxic manifestations or side-reactions are noted in dosages used. This particular combination of treatment seems more effective than dimercaprol alone.

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Multiple Ulcerations and Perforations of the Jejunum and Ileum Complicating Prednisone Therapy

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Corticotropic hormones and adrenal corticosteroids have proven to be the *sine qua non* of replacement therapy in certain pituitary and adrenal gland disorders. Although not a therapeutic panacea, the value of the induced hyperadrenal state in many additional illnesses has been established. Unfortunately, the occurrence of occasional deleterious side-reactions and untoward symptoms of overdosage have established their action to be as that of a "two-edged sword."

Among the complications of corticotropin and adrenal cortical hormone therapy, none are associated with a graver morbidity or higher mortality than are those involving the gastrointestinal system. The appearance of ulcerations of the duodenum and stomach with a high incidence of perforation and hemorrhage has been recognized with increased frequency and has led to a curtailment in the use of hormone therapy and to the use of a prophylactic ulcer regimen in cases where such therapy is mandatory. The hormones have resulted in the reactivation of old, healed ulcers and in the production of acute ulcerations in persons who never before had ulcers. In addition to the appearance of complications of the stomach and duodenum, a smaller number of reports describe ulcerations and perforations involving the jejunum, ileum, and large intestine.

A patient with nonspecific ulcerative colitis in the active stage developed multiple ulcerations and perforations of the small intestine shortly after commencing a course of therapy with prednisone. The case is presented along with operative and postmortem findings in view of the unusual nature of the complication. An analysis of this case along with a review of similar cases questions the etiological significance of altered gastric secretions and suppressed inflammatory response in the causation of all ulcerations and perforations of the gastrointestinal tract complicating hormone therapy. An alternate explanation for the occurrence of certain gastrointestinal complications secondary to corticotropin and adrenal corticosteroid hormone therapy is offered.

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Report of Case

A 63-year-old white man was hospitalized on March 3, 1956, with the chief complaint of diarrhea of six weeks' duration. Twelve to fourteen watery movements occurred per day. Although mucus was frequently detected in the stools, no blood was seen. Crampy, low abdominal pains occurred with ingestion of foods. Anorexia was present throughout the illness, and there was a 30 lb. weight loss.

Physical examination disclosed an emaciated white man, 5 ft. 9 in. tall, weighing 112 lb. Vital signs were normal. The chest was noted to be emphysematous. The abdomen was scaphoid in appearance and soft. No masses or organs were palpable. There was no tenderness to deep palpation. Peristalsis was normal. The remainder of the physical examination including digital rectal examination was unremarkable.

Admission hemoglobin was 14 gm. per 100 cc., and the leukocyte count was 13,600 per cubic millimeter, with a normal differential. Urinalysis was normal save for a trace of albumin. Serum electrolytes were normal. Numerous stools were found to be free of ova and parasites and were negative for enteric pathogens. Sputa smears and cultures were negative for acid-fast bacilli. The chest film showed early bilateral emphysema. A gastrointestinal series and barium-enema x-ray

taken elsewhere prior to admission were reviewed and found to be normal. The tuberculin skin tests were negative. Sigmoidoscopy disclosed a diffusely granular congested mucous membrane. Although no ulcerations were noted, gentle swabbing of the surface produced prompt bleeding.

Having established the diagnosis of acute, idiopathic ulcerative colitis, a course of adrenal corticosteroids was begun, hoping it would induce a prompt remission. On the seventh day of hospitalization, the patient was started on 40 mg. of prednisone per day, and by the sixth day of therapy the daily dose had been successively dropped to a maintenance level of 20 mg. per day. Coincident with the initiation of hormone therapy, improvement in the patient's clinical status was evident. By the ninth day of endocrine therapy the patient's bowel movements were reduced to two formed stools a day.

On the 10th day of hormone therapy, the patient experienced a sudden onset of severe generalized abdominal pain. Local spasm of the abdominal musculature was noted, and rebound tenderness was elicited. Although he remained afebrile, his leukocyte count promptly rose to 20,800 per cubic millimeter, and a differential showed 86 segmented and 2 nonsegmented neutrophils. A flat plate of the abdomen failed to show free air under the diaphragm. On the day of the gastrointestinal complication, the patient described having had a similar episode 48 hours before. He failed to call it to the attention of the ward physician because of its transient nature and its mildness. Emergency surgery was undertaken with a presumptive diagnosis of perforated viscus, due to an acute ulcer either of the stomach, the duodenum, or the large intestine. Intravenous hydrocortisone was given before and during the operative procedure. The laparotomy disclosed the presence of numerous ulcerations, all of which were confined to the antimesenteric border of the small bowel. They extended from the ligament of Treitz to the ileocolic junction. Five had perforated in the region of the jejunum. The proximal 52 cm. of jejunum was resected (Fig. 1) and an end-to-end anastomosis done. The remaining ulcers were plicated with fine nonabsorbable (silk) surgical sutures. The serosa between the ulcerations appeared normal, and no pathology in the stomach, duodenum, or colon was noted. The blood supply to the bowel did not appear compromised.

Postoperatively, the patient ran an unexpectedly benign course. His temperature, pulse, and respirations remained normal and his abdomen soft. Formed bowel movements occurred, and on the third postoperative day the patient was ambulatory and taking oral fluids. On the fifth postoperative day minimal deterioration of the patient's condition was noted, and because of lethargy the question of adrenal insufficiency was considered. The vital signs were found to be normal, and local abdominal findings were unchanged. Repeat hematology and electrolyte studies showed no alterations. On the sixth postoperative day, the patient suddenly and unexpectedly died.

Fig. 1.—Resected section of jejunum from serosal surface, showing multiple ulcerations and perforations.

Pathology Report

Surgical Specimens.—The specimen consisted of a 52 cm. segment of jejunum (Fig. 1). The serosa was injected, granular, and edematous throughout. The muscularis appeared somewhat thin. The mucous membrane in general appeared normal, except for the presence of 19 ulcers, which averaged 0.4 cm. in diameter. These ulcers had flat, irregular margins, were irregularly round in contour, were shallow, and were covered by a purulent exudate. Five of the ulcers penetrated the entire thickness of the bowel wall (Fig. 2), and the peritoneal margins were covered by purulent material. Microscopically, the ulcers showed necrotic bases and margins, with dense infiltration of these areas and adjacent tissues by neutrophiles, histiocytes, plasma cells, and lymphocytes (Fig. 3). The margins of the ulcerated areas showed vascular granulation tissue and no appreciable scarring. Serosa throughout was edematous, with a narrow zone of vascular granulation tissue in subserosal areas and infiltration by mixed inflammatory cells. Intervening areas showed mucosal and submucosal edema and congestion, with infiltration by mixed inflammatory cells. Cultures of ulcerated areas were negative for fungi, tuberculosis, Salmonella, and Shigella organisms. Growth of enterococci and coliform organisms was obtained.

Autopsy Findings.—The body showed evidence of recent weight loss and a recent right para-

Fig. 2.—An acute ulcer of jejunum with adjacent normal mucous membrane. A small free perforation is noted.

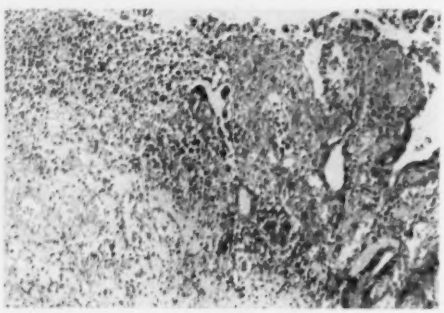

Fig. 3.—Base of acute ulceration, showing inflammatory response and early granulation tissue formation.

median surgical incision. The lungs were emphysematous and anthracotic, with acute and chronic passive congestion and small foci of interstitial fibrosis. The heart showed considerable coronary arteriosclerosis, with scattered small myocardial scars. Major arteries and veins, including the mesenterics, were patent and of normal caliber. The peritoneal cavity contained 600 ml. of purulent and fecal material. All peritoneal surfaces were ragged and granular, and there was considerable autolysis of bowels. The stomach was greatly dilated, with a thin wall and flattened rugae. There was an intact end-to-end anastomosis involving the proximal jejunum. There were numerous ragged and irregular perforations of the walls of the ileum and residual jejunum. Microscopically, the small bowel in general showed interstitial edema, congested blood vessels, and distended lymphatic channels and a few scattered infiltrating lymphocytes, histiocytes, and neutrophils. There were scattered acute ulcerations with adjacent degenerative changes in epithelial and stromal elements. Blood vessels showed moderate thickening of the walls, and lymph follicles showed depletion of lymphocytes. The large bowel had a thin and friable wall, with no perforations or ulcerations. Microscopically, there was autolysis of mucous membrane, submucosal edema, and congestion, with neutrophilic infiltration of submucosa and muscularis. All peritoneal surfaces showed acute inflammation, with beginning formation of granulation tissue in subserosal areas. There was a mild, fatty metamorphosis of the liver, with acute and chronic passive congestion and a few neutrophils in sinusoids and portal areas. There was moderate depletion of adrenal cortical lipid material. Pancreas and thyroid appeared normal. The spleen weighed 75 gm., showing depletion of lymphocytes in follicles. Mesenteric lymph nodes were enlarged and soft, microscopically showing reactive hyperplasia. Lumbar vertebral marrow revealed hyperplasia, chiefly involving the erythrocytic elements. There was moderate arterial and arteriolar nephrosclerosis, and the prostate gland was large and hyperplastic. The testes showed slight atrophy.

Comment

The frequent relationship between emotional disturbances and acute stresses and exacerbation of peptic ulcer symptoms has been recognized. The effects upon the gastrointestinal tract of nervous and emotional stresses have been the subject of numerous investigations and have been responsible for the statement that the gastrointestinal tract is the "sounding board of the emotions." It has been shown that stresses productive of the "alarm reaction" can produce acute gastric and duodenal erosions. The most common sources of such stress are thermal burns, trauma, and surgery. More recently, papers have reported ulcerations following severe starvation [1,2] and exposure to ionizing radiation.[3] The relationship between acute lesions of the alarm type and chronic peptic ulcer has not been established. Their gross and microscopic appearances and their natural history differ. Selye [4] stated, "We must differentiate clearly between the acute gastro-intestinal erosions and hemorrhages caused by such alarming stimuli as burns, trauma, fulminating infection, and intoxication, etc., on the one hand, and the chronic peptic ulcer on the other." It is felt, however, that there is a closer relationship between stress ulcerations seen in clinical practice and those that appear following therapy with pituitary corticotropic and

adrenal cortical hormones. The former presumably result from an excess production of endogenous hormone produced via stress-mediated stimulation of the hypothalmic-pituitary adrenal axis.

Most reports of gastrointestinal complications of corticotropin and cortisone therapy have attempted to explain their appearance on the basis of a hormonal phase of gastric secretion. Gray et al.[5-7] did much to establish an adrenal phase of gastric secretion. They showed that the administration of pituitary corticotropic and cortisone hormone to normal subjects produced an increase in the uropepsin excretion to levels ordinarily seen in patients with active peptic ulcers. Following intravenous corticotropin, uropepsin excretion in urine increased from control values of 4000 units to 16,000 units per 24 hours. With oral cortisone, the uropepsin increased to 113% and 300%. An equally significant increase in basal gastric secretion of acid and pepsin followed hormone therapy, the latter representing a threefold increase. The action of the adrenal corticoids on the stomach is a direct one and is not mediated through the vagus, nor is it dependent on the gastric antrum. This has been shown, for vagotomy does not alter gastric acid or pepsin response to hormonal therapy, nor does subtotal gastric resection with removal of the antrum.

An alteration of acid and pepsin secretion in response to corticotropin and cortisone has not been universally accepted as being responsible for the production of gastrointestinal complications. Hirschowitz et al.[8] studied gastric response before, during, and after administration of corticotropin. Although they recognized that hormonal administration stimulated gastric secretion of acid and pepsin and that such therapy may be complicated by the development or reactivation of a peptic ulcer, they pointed out that it did not necessarily follow that the increase in secretion is the cause of the ulceration. Since the abnormal rise in secretions did not occur prior to the appearance of the ulceration, excessive peptic activity could not be incriminated as the cause of the ulcer. They did note that corticotropin stimulation of the adrenal gland caused a profound and consistent fall in the viscosity of the gastric juice as well as a decline in the viscosity and mucus content. They felt that corticotropin may interfere with the natural defense of the mucosa and so play an important part in the exacerbation of and healing of peptic ulcerations.

In addition to an altered gastric secretion induced by hormonal therapy, an inhibition of tissue reaction to injury has been considered etiologically related to the development of the gastrointestinal complications. Ironically, it is that very same anti-inflammatory reaction of corticotropin therapy that constitutes the common denominator of its clinical effectiveness in all conditions except the few where replacement therapy is practiced. The untoward gastrointestinal complications occurring secondary to an induced hyperadrenal state are often characterized by a sparsity of subjective and objective findings. There is often an absence of febrile and leukocytic response; a tachycardia and elevation of sedimentation rate fails to appear, and the local findings of muscular rigidity and rebound tenderness are often absent. Ragan[9] was one of the first to note a delay in wound healing in patients receiving hormone therapy. The mechanisms by which corticotropin influences inflammation and adversely affects the healing process are multiple. After administration of hormones the number of leukocytes and eosinophils at the site of inflammation is diminished. The outpouring of cells and serum into the site of irritation is diminished by an increase in capillary resistance induced by hormone therapy. The healing of any ulceration or inflammation is dependent on the formation of healthy granulation tissue at the base of the site of injury. Corticotropin has been shown to depress formation of all elements of granulation tissue; fibroblasts, blood ves-

sels, and the ground substance.[10-12] It has also been shown to retard the process of epithelization.

Reports in which gross or microscopic descriptions of lesions of the stomach and duodenum secondary to hormonal therapy are undertaken frequently show a characteristic decrease of defense mechanisms aimed at repairing and limiting the extent of the ulceration. Sandweiss,[13] describing such ulcerations, commented, "The usual defense mechanisms are markedly depressed or absent; the ulcers are more recent, far more acute, more rapidly spreading and at times much larger than those usually seen in ulcer patients."

Perforations of the bowel distal to the duodenum have occurred during hormonal therapy and no longer represent unique problems. Such accidents have most frequently occurred subsequent to treatment for ulcerative colitis and have involved either the colon or the terminal ileum. Additional isolated reports described perforation in an area of regional enteritis,[14] in a diverticulum of the colon,[15] and at the site of bowel involvement with intestinal Hodgkin's disease.[16] Another report [17] described perforation of a gallbladder in a patient on hormone therapy. All had in common a preexisting diseased bowel at the site of subsequent perforation. The maintenance of integrity of a diseased bowel is dependent upon a balance between tissue destruction and tissue repair. The action of cortisone, mediated through its inflammatory inhibition, alters the balance in favor of the former. That the accidents of ulceration and perforation can occur in the absence of exogenous hormone is attested to by the finding of perforations in the era prior to corticotropin and cortisone therapy and by their occasional occurrence today in the absence of hormone treatment.

The reports of the appearance of ulcerations or perforations distal to the duodenum and yet remote from areas of disease are few but highly significant. They afford evidence against the hypothesis of autodigestion by gastric juices and against interference in the repair process of a preexistent diseased bowel. That the case described is not unique is attested to by the following case reports culled from the literature. In 1952, Johnsen [18] reported a spontaneous perforation 12 cm. below the duodenojejunal flexure in a patient with Cushing's disease. Finck [19] studied an arthritic patient who died subsequent to a prolonged course of self-medication with cortisone and found a duodenal ulcer and numerous mucosal erosions of both the stomach and the small intestine. Sauer [14] commented on the appearance of two large shallow ulcers encircling the rectal wall in a patient on prolonged hormonal therapy for arthritis. Brown [20] observed two patients with severe rheumatoid arthritis who, subsequent to cortisone treatment, developed "ragged atypical ulcers all through the colon." While all the patients just described were free of any preexisting disease of the gastrointestinal tract, the following cases demonstrated complications occurring in patients with ulcerative colitis. In the cases to be described, the sites of ulcerations either occurred remote from the diseased process or were found to be of a type not characteristic of that disease process.

During surgery, on a patient with ulcerative colitis who was receiving hormonal therapy, Halsted [21] noted "large discrete ulcers of the ileum." In one of Sloan's [22] patients, an acute abdomen appeared during corticotropin therapy. At the time of surgery, four perforations of the gastrointestinal tract were noted, two in the terminal ileum and two in the jejunum. Texter [23] described the appearance of "giant ulcerations" appearing subsequent to corticotropin and cortisone therapy in 4 of 16 patients with ulcerative colitis who were receiving hormonal therapy. The large undermining ulcers noted were described by sigmoidoscopy and x-ray as being of an appearance "distinctly different from what is usually seen in cases of colitis without cortisone treatment."

While most patients started on corticotropin or cortisone therapy show clinically a dramatic reversal of the unfavorable progression of the disease, a few show no response. Fewer still show an accelerated deterioration. Banks and Klayman [24] noted prompt onset of serious hemorrhage in each of three cases of colitis after starting therapy. One patient with a previous attack of colitis had been completely well for two years when therapy with cortisone for rheumatic arthritis was begun. A fulminating bout of hemorrhagic diarrhea occurred on the sixth day of therapy. Halsted's [25] Case 4, a patient with ulcerative colitis who had never previously bled, developed severe bleeding which lasted four days one week after administration of 25 mg. of corticotropin daily. Cases 3 and 19 of Elliot [26] developed severe hemorrhage during corticotropin therapy at a time when they appeared to be doing well in regard to their ulcerative colitis. One had a history of previous hemorrhage, the other did not. Edwards,[27] drawing attention to the danger which accompanies the use of hormonal therapy, stated: "In one center, four consecutive examples of massive bleeding had occurred during treatment of chronic ulcerative colitis by ACTH." Where untoward reactions of this type described follow institution of hormone therapy, the complications might result from a retarding of healing of the ulcerative lesions of colitis. That they might have been unrelated to a preexisting pathology and were due to the appearance of new lesions of the type that occasionally occur in nondiseased segments seems possible.

Ulcerations and perforations appearing during corticotropin and adrenal cortical hormone therapy have been reported to involve the stomach, duodenum, jejunum, ileum, and colon. Although the different ways in which a tissue can react to injury are limited, the similarity in the gross and microscopic appearances of the lesions in different segments of the gastrointestinal tract, the occasional finding of multiple sites of involvement, and their occurrence during similar therapy suggests a common etiology of the more commonly seen ulcerations of the stomach and duodenum and the unusual lesions found distal to the duodenum.

The explanations usually offered to account for the appearance of gastrointestinal ulcerations of the stomach and duodenum during hormone therapy do not appear tenable in the case presented. That altered gastric secretions induced by use of hormones were not primarily related to their development is attested to by the locations of many of the lesions remote from exposure to unneutralized gastric secretions. The finding of a normal, intervening mucosa in the proximal jejunum and the development of equal numbers of lesions in both the proximal jejunum and distal ileum casts doubts on the likelihood of altered gastric secretion being etiologically related to their formation. If due to an outpouring of gastric juices into the small bowel, one would have expected extensive involvement of the proximal part of the small intestine with absent involvement of the more distal parts. In the reported case, the distribution of ulcerations in the 52 cm. of resected jejunum was constant, and additional ulcerations were found to extend all the way to the ileocolic junction. If the pathology had been due to the digestive action of stomach secretions, instead of finding well-circumscribed ulcerations with normal intervening mucous membrane, as was noted in our case, the appearance of a more diffusely necrotic area would have been seen.

The findings of ulcerations and perforations unrelated to sites of preexisting pathology fail to defend the importance of altered repair of diseased tissues in their development. The finding of a prompt leukocytic response, along with the physical findings of an acute peritonitis following the perforations, failed to substantiate the existence of a suppression of inflammatory response. Furthermore, the microscopic findings of the resected jejunum, removed shortly after perforation, demonstrated a normal invasion by inflammatory cells and a prompt appearance of granulation tissue

around the margins of the perforations and in the bases of the ulcerations.

A single satisfactory explanation for the development of gastrointestinal complications of corticotropin and adrenal hormone therapy is lacking and will probably not be forthcoming. More likely there are several contributing factors operating to produce or to prevent the occurrence of ulcerations. Included are autodigestion by secretions produced by the entire gastrointestinal tract and accessory organs and an alteration of the natural defenses of the mucosa, the latter secondary to a decrease in mucus production and an inhibition of inflammatory response to injury. Additional etiological factors probably exist, and our ignorance of their pathogenesis results in our utilizing such statements as "susceptible mucosa" and "constitutional predisposition." The duration of hormone therapy and the dosage are apparently of little significance in predicting occurrence of complications.

A characteristic feature of all living tissue is the continuous process of death of cells and replacement by growth of new tissues. The latter process is dependent on the maintenance of an equilibrium or of positive nitrogen balance. The continuous secretion and absorption of enzymes, water, and electrolytes along with trauma of peristaltic activity and exposure to intestinal contents expose the gastrointestinal tract to considerable "wear and tear." The extent of cellular exfoliation and the great number of mitotic figures normally noted along the intestinal tract attest to the dynamic state of the mucus membrane of that system. The cytotoxicity of antileukemic agents is manifest in tissues demonstrating a high rate of metabolism. In addition to causing a hypoplasia of bone marrow, ulcerations of the gastrointestinal epithelium are frequent toxic findings and reflect the increased metabolism of the epithelium of that system. In the presence of increased body catabolism and impaired growth of tissues, the more rapidly growing or metabolizing tissues suffer more than the more quiescent tissues.

By the time hormonal therapy is utilized in a given patient, the recipient often presents a state of advance inanition secondary to decreased intake of protein and increased destruction of tissue. The integrity of the bowel wall reflects the state of depletion manifested by his external appearance. The effect of glucocorticoids on protein metabolism appears to play an important role in the development of gastrointestinal complications secondary to hormonal therapy. That they have a duel action has been recognized, one being an inhibition of protein synthesis and the other a catabolic effect manifested by a mobilization of tissue protein. The stage is thus set by the chronic illness and the additional metabolic insult of hormone therapy leads to the complication of further loss of tissue integrity and eventual ulceration. Studying children, Blodgett et al.[28] found that cortisone tends to slow the growth within a few weeks of onset of therapy. The gain in weight and sense of well-being following hormonal therapy belies the detrimental effect excessive adrenal corticoids have on the tissues of the body. An excessive endogenous production of adrenal hormones produced by the stress of the initial pathologic process prior to institution of therapy compliments the subsequent action of hormone therapy. Findlay and Howes[29] showed that the direct tendency toward delayed healing caused by cortisone is augmented by a preexisting state of protein depletion. The patient reported represented an advanced state of debility at the time hormonal therapy was initiated. The findings in this case of ulcerations on the antimesenteric border of the bowel at the site of relatively poor circulation is consistent with the hypothesis which stresses the etiological importance of altered protein metabolism on the development of ulcerations complicating hormone therapy.

The use of adrenal corticosteroids in the initial therapy of ulcerative colitis has been questioned, and in the case under discussion therapy was initiated with some trepidation.

Hormone therapy was utilized, realizing it would probably arrest the acute and progressive process promptly which, within a short period, had converted the patient from a healthy, gainfully employed person to one who was debilitated and acutely and chronically ill. Regarding the use of hormones, current practice calls for utilizing large initial doses, hoping a remission will be promptly induced. The management of the case under discussion reflected that mode of therapy. The authors are of the opinion that large initial dosages of hormones are probably unnecessary in most cases and are potentially dangerous in patients whose physical states reflect a marked degree of protein depletion.

As one reviews the literature, it becomes apparent that although the newer and more potent cortisone and hydrocortisone derivatives have a lessened salt-retaining effect, their use is accompanied by a higher incidence of ulceration and perforations of the gastrointestinal tract. Therefore, the hormones of choice in patients where electrolyte disturbances are not anticipated and where catabolic activity is especially undesired are cortisone and hydrocortisone, not their synthetic derivatives, prednisone and prednisolone. The concomitant use of anabolic hormones, either estrogens or testosterone or a combination of both, and the maintenance of a high protein intake should be practiced with adrenal corticosteroid therapy.

Summary

A patient with acute ulcerative colitis developed multiple ulcerations and perforations of the jejunum and ileum shortly after commencing a course of therapy with prednisone. The etiological significance of altered gastric secretions and suppressed inflammatory response in the causation of the complicating lesion is questioned. In the case presented the protein catabolic effect of the induced hyperadrenal state probably potentiated the already existent tissue inanition and led to loss of tissue integrity and ulcerations.

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Books

EDITED BY WILLIAM B. BEAN, M.D.

Treatment of Heart Disease: A Clinical Physiologic Approach. By Harry Gross, M.D., F.A.C.P., and Abraham Jezer, M.D. Price, $13.00. Pp. 549, with 91 illustrations. W. B. Saunders Company, 218 W. Washington Sq., Philadelphia 5, 1956.

This book deals with the major types of heart disease and their complications, with a discussion first of the pathologic physiology involved and then the treatment. The latter is gone into in some detail. The first part has to do with basic mechanisms. It delves extensively into the pathologic physiology of myocardial insufficiency, and it includes chapters on the arrhythmias, digitalis and quinidine, and diet in heart disease. The bulk of the book is concerned with specific types of heart disease. The book is adequately illustrated, principally with x-rays and electrocardiograms (there is an abundance of the latter). Rather curiously, the illustrations are not referred to in the text. There is a long list of references at the end of each chapter and an appendix of diets, menus, etc. at the end of the book.

The authors' objective of going over the pathologist physiology forming the basis for treatment is a commendable one and is followed conscientiously. Treatment is described thoroughly, often with exact doses of drugs. Procedures, e.g., pericardicentesis, are described in detail. The book should therefore be of considerable practical value to clinicians. I liked the summaries at the end of many of the chapters and sections. The book is written in a manner easy to read. However, occasional statements are not clear, e.g., "The lack of any specific action of salicylates on the sedimentation rate is clearly demonstrated by the prompt rise in the sedimentation rate following discontinuation of the drug" (p. 273). In the same section the statement, "The salicylates increase the sedimentation rate of the red cells . . ." seems to contradict what has just been said in the preceding paragraph (p. 274). A few other errors or apparent errors should be pointed out. The statement (in discussing circus movement), "When the circuit time is greater than the refractory period, the atrial tissue fails to respond to the impulses" not only is incorrect but does not follow from preceding statements (p. 71). The statement "Glomerular filtration is also impeded by increase in renal venous pressure" (p. 355) is questionable and does not agree with Fishberg ("Hypertension and Nephritis," 1954, p. 26). I found the authors' use of "volumes percent" in referring to hemoglobin concentration (pp. 330 and 367) somewhat puzzling. On page 141, 40 gm. of mercury is apparently a typographical error.

These are minor criticisms. The task of writing a book of this sort is a difficult one, and it seems to me the authors have done it well. All physicians should find the book of interest and value.

GEORGE F. CLABAUGH, M.D.

Human Perspiration. By Yas Kuno. Price $9.50. Pp. 416, with illustrations. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill., 1956.

There are two environments which determine our reactions to the weather—our internal environment and the heat, moisture, and air movement of the world about us. Except as a perennial conversation piece for breaking social ice jams, few people know or care why or how "weather" makes them perspire. They are simply annoyed by it. With the exception of the unhappy victims of ectodermal dysplasia, we all get in a sweat sometime or other, and this is the classic book which tells us all about it. The original edition, published in 1934 by a devoted scholarly Japanese investigator, Kuno, has long been out of print. It was established immediately as the definitive study of human perspiration. Anyone interested in problems of acclimatization and adaptation to heat went to this as a source of thoroughly grounded research. The whole problem has been neglected pretty generally by physicians, though many patients cannot be treated properly without clear understanding of the effects of heat on them in bed, at operation, or during recovery, by day and by night.

This new edition, completely rewritten, is notable because it summarizes a large new body of data arising from studies done during World War II and since that time. Such studies

have carried solutions one or several stages further along in some aspects of the problem, but still the massive contribution to the work came from Kuno's own laboratory. It is rare today in physiology and medicine for anyone to dominate any field so completely, let alone so well as Kuno has dominated research in human perspiration.

The structure, mechanisms, distribution, variation, and function of units of the sweating apparatus are explained and illustrated with comprehensive skill. He describes the two remarkable phases of acclimatization—first the change which makes sweating begin more promptly on exposure to heat along with the increased volume of sweat which accompanies the rapidly gained cardiovascular thermal adaptation, and then a slower salt-saving change mediated by the adrenal cortex—which constitute the two adaptations. Perhaps months or years later gradually a sweat-conserving process may become established, at least in tropical countries. Then less sweat is produced for a given heat stimulus. This is important, since sweat which cannot evaporate has its cooling function largely wasted. The exhaustion of sweating mechanisms, acutely in heat stroke, more gradually in a state resembling cumulative fatigue, which was first established during World War II, is ably discussed. It may cheer those who resist the mental repose prevalent in devotees of the all-encompassing systems to know that Kuno has not needed to invoke the terms or concepts of "stress."

The explanation for the uneven intensity of sweating on the palm as being the result of repeated pressure is inaccurate if the photograph is correct, since at least at the distal part of the palm sweating is most intense between and not at the exact site of the normal pressure points. Most sweating actually occurs on the palms in areas where palmar erythema presents its most intense redness.

If Kuno himself wrote the book he has better mastery of medical English than most persons writing in this country today. If a translator did it, praise for his excellence will be hidden under the oblivion of total obscurity. There are more typographical errors than par for the course in this book, perhaps because in a foreign language it is more difficult to find mistakes. Many references noted in the text are not included in the rather brief bibliography. An occasional sentence has a turn or usage perhaps Japanese, certainly not American. On a certain page "pudendal" emerges as "prudental," perhaps wisely but not too well. The habit of forecasting what will appear later as "See page 250," etc., is a little annoying and probably unnecessary, but these are trivial specks in a monumental study of a vital but simple problem which is all too often neglected. Here it is approached by the simple tools of observation, logic, and experiment in a classic book which again will assume its domination of the field.

WILLIAM B. BEAN, M.D.

Pathologic Physiology: Mechanisms of Disease. Ed. 2. Edited by William A. Sodeman. Price, $13. Pp. 963, with 173 illustrations. W. B. Saunders Company, 218 W. Washington Sq., Philadelphia 5, 1956.

Some months ago, hard pressed to define the peculiar genus "internist," I described him as a general practitioner of medicine attempting to pursue his art without benefit of instruments beyond those required for physical examination, plus the hypodermic syringe and book of prescription blanks. I might have added that to be a good internist or teacher of medicine he needed more than a passing acquaintance with the kind of knowledge contained in Sodeman's text.

With today's insistence on understanding of the reasons behind abnormal functioning of tissues and organs rather than a chief reliance on the morphologic changes detected grossly or microscopically by the pathologist, physiology takes its place as the primary discipline of the student of medicine. No longer will a thorough knowledge of the history, etiologic factors, pathologic changes, and clinical manifestations of an abnormal physical condition suffice in explaining a disease process to students, patients, or the physician himself. It is precisely here that books such as Sodeman's are required to supplement the presentations found in ordinary textbooks of medicine. Full cognizance of this need and an attempt to tell "how the patient got that way" are evident in the current textbooks of medicine. But lack of space and lack of the excellent organization found in the Sodeman text make their coverage of pathologic functioning inadequate.

A galaxy of talent has been assembled to deal expertly with the wide fields of knowledge that must be encompassed in a volume on pathologic physiology. I was particularly impressed with the section on water balance, by Pullen and Rushmer; the discussion of the effects of physical, toxic, and chemical agents on the body economy, by Bean; the entire discussion of

the circulatory system, by Sodeman, Roberts, Hall, and La Due, and the urinary tract, by Corcoran and Page. The other sections are handled with equal skill and authority.

If one book were to be singled out as the most important for preparing a candidate for examinations for the Board of Internal Medicine, this probably would be it—not because it contains more factual knowledge than any other, but because it presents the kind of knowledge internists need for their particular job. For the same reason it will doubtless be popular with most medical teachers. For some practitioners seeking an outline of what to do in a given situation it will be less valuable than a standard textbook of medicine, where statements are more dogmatic. The book is well printed and well illustrated. In a few sections, notably those dealing with infections, a more extensive bibliography would have been desirable. Taken altogether, it is an outstanding collection of monographs of which each author may well be proud.

PAUL S. RHOADS, M.D.

The Image of the Heart and the Principal of Synergy in the Human Mind. By Daniel E. Schneider, M.D. Price, $6. Pp. 267, with illustrations. International Universities Press, Inc., 227 W. 13th St., New York 11, 1956.

I should advise internists not to read this book unless they subscribe wholeheartedly and uncritically to the faith of psychoanalysts. The theme might fascinate anyone, and especially physicians and internists. Unfortunately, the whole religious dogma and jargon of Freudian psychoanalytical psychiatry demonstrate in standard form basic inability to separate strong and well-presented convictions from established facts. While hypotheses are useful, and theories valuable, facts are essential. In short, despite the elaborate employment of abstruse mathematical formulae and a number of studies which at least give lip service (should I say oral service?) to ordinary physiologic concepts and to clinical investigation, there is no clear separation of word, idea, and thing. No doubt the author's thesis has an element of truth. There may be a representation within us—some kind of physical nidus for sound with the heart as its conceptual center. The idea of the heart as symbolic of the genitals would occur, I believe, only to someone who was so haunted by sex symbolism that any object of any dimension, size, or shape might be identified as gonadal. We see what we look for, not necessarily what is there.

I have no doubt that this book will please psychoanalysts, at least some of them; but this is a glaring example of the fact that many psychoanalysts, at least those who write a great deal, are no longer clinicians or physicians. They are specialists who have left concepts of physiology and medicine somewhere in the distance.

I am not willing to believe that the laws of logic, of evidence, and of biology cannot be applied to the extremely difficult problems of psychiatry, and even those of psychoanalysis. Granted, it may be impossible to get a series of true controls in such a complex field; nevertheless, success of the method in predicting must be established if there is ever to be any demonstration of validity. I would like to see as few as ten patients examined by those who believe in ideas expressed in this book and have predictions made as to who would have a heart attack, what kind, and when. So far it is all post hoc. Lacking such evidence, we can only conclude that the value of this book for internists and cardiologists is measured by the five lines with which the author disposes of cholesterol. Even in the interesting study of combined electrocardiography and electroencephalography, one finds no mention and apparently no thought of a control study using the same preparatory drugs, etc. One marvels at sudden death and a postmortem examination which showed "nothing but acute coronary closure and no pre-existing disease." The words and notions of cybernetics float back and forth, feeding forward more often than back in uncontrolled fashion, and do not even seem to form a real image in the "integrative sonic—ultrasonic barrier—theoretically described as existing in the human nervous system basically mediated by the solitary nucleus and solitary tract and their various connections to the brain and to the body." The whole effect of this book on my nervous system, such as it is, resembles that which Schneider relates in the brutal childhood of Edgar Allen Poe who is described as being "fed on alcohol soaked in gin." This is too strong medicine for most of us. My recommendation is keep off.

WILLIAM B. BEAN, M.D.

News and Comment

ANNOUNCEMENTS

Symposium on Venereal Diseases.—The eighth annual Symposium on Recent Advances in the Study of Venereal Diseases will be held in the auditorium of the Department of Health, Education, and Welfare, Washington, D. C., on April 24-25, 1957.

The sessions are open to all interested physicians and workers in allied professions. Hundreds of participants from all parts of the country, including many outstanding authorities on venereal disease, attend annually to exchange the latest available information.

Topics to be discussed will cover many aspects of venereal disease control, including basic and clinical research, serology, epidemiology, treatment, program operation, and professional education.

Venereal Disease Postgraduate Conference.—The 26th Venereal Disease Postgraduate Conference for physicians, sponsored by the University of Tennessee College of Medicine and the Public Health Service, will be held at the College of Medicine in Memphis, April 18-20, 1957, inclusive.

The course is designed to acquaint the practitioner with the latest developments in diagnosis, treatment, and management of the venereal diseases. No tuition will be charged. Applications for admission are to be sent to Dr. Henry Packer, Department of Preventive Medicine, University of Tennessee College of Medicine, Memphis 3.

Discussion leaders for the course will be drawn from university faculties, Public Health Service personnel, and other outstanding authorities in the field.

Fellowship in Cardiology.—A fellowship in cardiology is available at the Veterans Administration Hospital, 42d & Clement St., San Francisco 21, on July 1, 1957. The fellowship is supported by the San Mateo County Heart Association, the fellow being appointed from Stanford University School of Medicine. The stipend is $300 per month, the appointment for one year. Appointments are renewable. Applicants must be graduates of Class A medical schools and citizens of the United States.

Several fellowships are also available in hematology and chemotherapy of tumor and lymphoma, in conjunction with Stanford University School of Medicine. Stipend begins at $300 per month. Fellowships are supported by the National Institutes of Health in conjunction with a research project. Those interested should address inquiries to Dr. Forrest M. Willett, Chief, Medical Service, at the above address.

American Goiter Association.—The 1957 meeting of the American Goiter Association will be held in the Hotel Statler, New York, May 28, 29, and 30, 1957.

The program for the three-day meeting will consist of papers and discussions dealing with the physiology and diseases of the thyroid gland. Address inquiries to John C. McClintock, M.D., Secretary, 149½ Washington Ave., Albany 10, N. Y.

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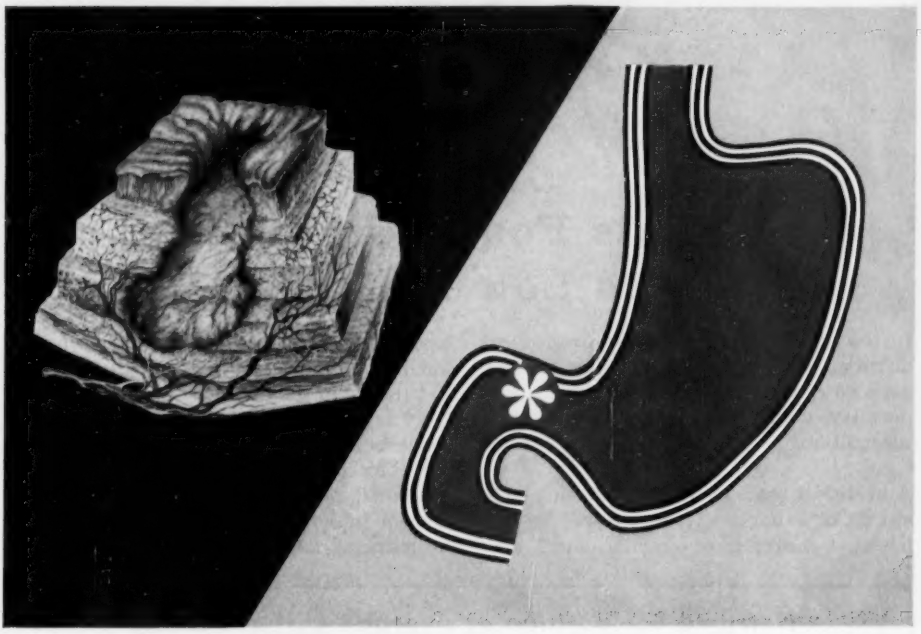

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A breakfast main dish, a food serving consisting of 1 ounce of ready-to-eat or hot cereal, 4 ounces of whole milk, and 1 teaspoon of sugar has a well-merited place among those considered for reducing the fat intake in the diet as shown below. *Not only is this portion low in fat and low in cholesterol but it makes a worth-while contribution of complete protein, essential B vitamins, and minerals.* Thus it merits inclusion in dietary regimens for the purpose of reducing fat in the diet.

Nutritive Composition of Average Cereal Serving

	Cereal, 1 oz. Whole Milk, 4 oz. Sugar, 1 teaspoon	Cereal** 1 oz.	Whole Milk 4 oz.	Sugar 1 teaspoon
Calories	203	104	83	16
Protein	7.3 gm.	3.1 gm.	4.2 gm.	
Fat	5.3 gm.	0.6 gm.	4.7 gm.*	
Carbohydrate	32.2 gm.	22 gm.	6.0 gm.	4.2 gm.
Calcium	0.169 gm.	0.025 gm.	0.144 gm.	
Iron	1.5 mg.	1.4 mg.	0.1 mg.	
Vitamin A	195 I. U.	—	195 I. U.	
Thiamine	0.16 mg.	0.12 mg.	0.04 mg.	
Riboflavin	0.25 mg.	0.04 mg.	0.21 mg.	
Niacin	1.4 mg.	1.3 mg.	0.1 mg.	
Ascorbic Acid	1.5 mg.	—	1.5 mg.	
Cholesterol	16.4 mg.	—	16.4 mg.*	

*Nonfat (skim) milk, 4 oz., reduces the Fat value to 0.1 gm. and the Cholesterol value to 0.35 mg.

**Based on composite average of breakfast cereals on dry weight basis.

Bowes, A. deP., and Church, C. F.: Food Values of Portions Commonly Used. 8th ed. Philadelphia: A. deP. Bowes, 1956.
Cereal Institute, Inc.: The Nutritional Contribution of Breakfast Cereals. Chicago: Cereal Institute, Inc., 1956.
Hayes, O. B., and Ross, G. K.: Supplementary Food Composition Table. J. Am. Dietet. A. 33:26, 1957.

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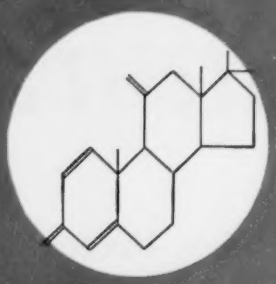

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1 Bollet, A.J., Black, R., and Bunim, J.J.: J.A.M.A. *158*:459 (June 11) 1955.

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References: 1. Krieg, W. J. S.: Functional Neuroanatomy, Philadelphia, The Blakiston Company, 1947, pp. 111-133. 2. Kinney, J. J.: J. M. Soc. New Jersey *53*:128 (March) 1956. 3. Weil, L. L.: Florida J. Gen. Pract. *4*:9 (July) 1954. 4. Report of Study by Army, Navy, Air Force Motion Sickness Team: J.A.M.A. *160*:755 (March 3) 1956.

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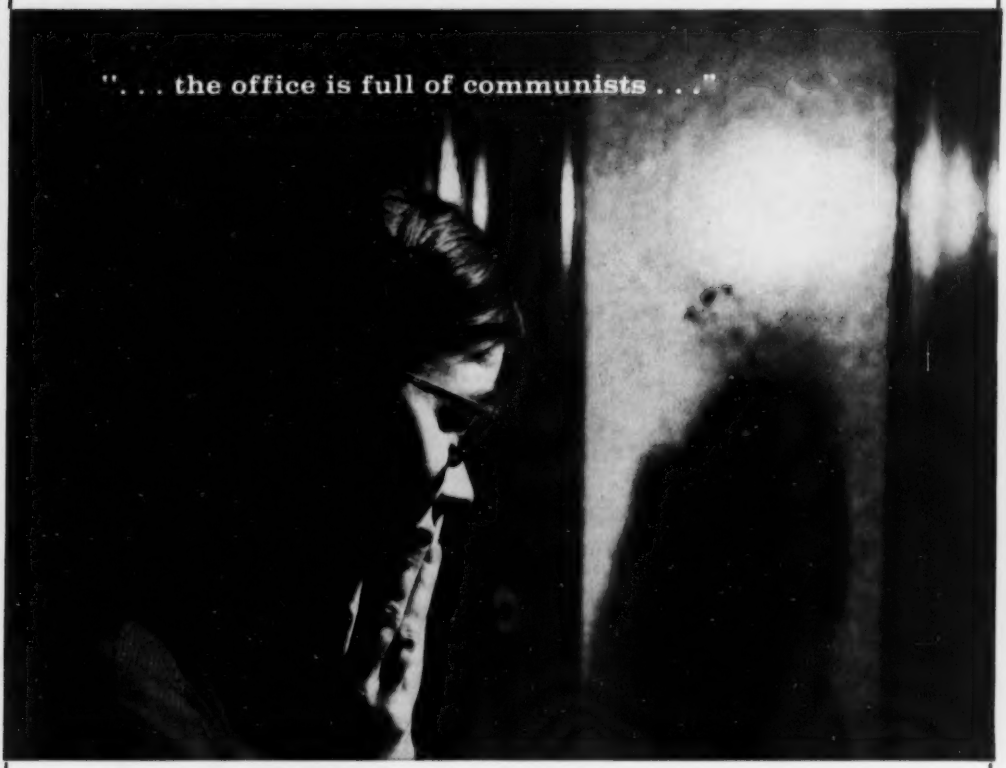

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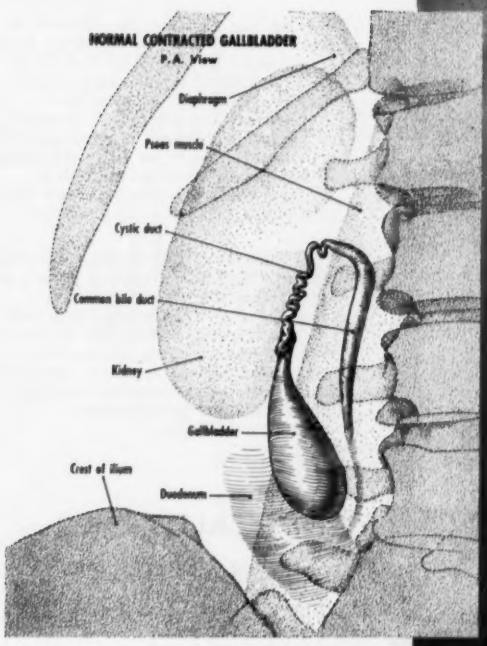

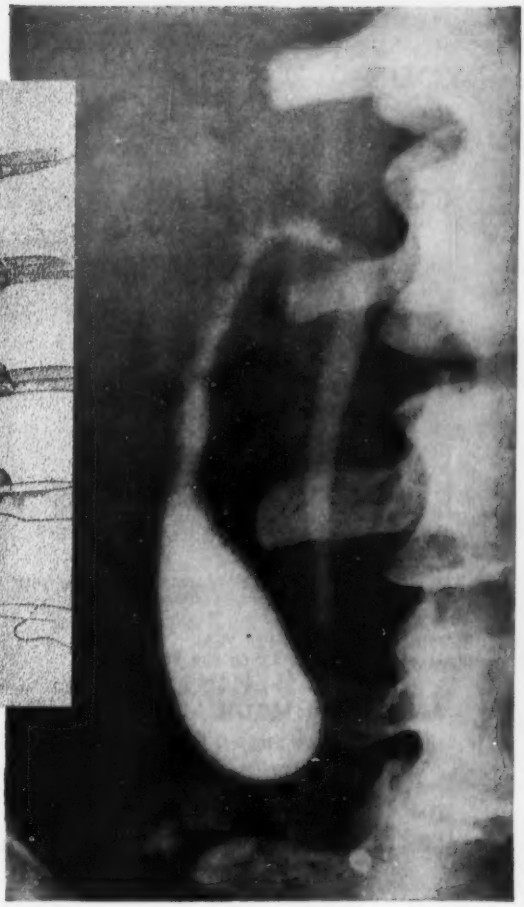

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Buckstein, Jacob: The Digestive Tract in Roentgenology. Philadelphia, J. B. Lippincott Co., 2nd ed., 1953, vol. 2, p. 1003.

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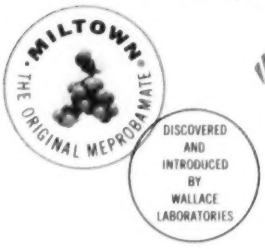

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Pennington, V. M.: J.A.M.A. In press, 1957.

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Altschul, A. and Billow, B.: New York State J. Med. In press, 1957.

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Gillette, H. E.: Internat. Rec. Med. 169: 453, 1956.

4 "Complications associated with long-term therapy are probably seen in lowest incidence with meprobamate ['Miltown']."

Fazekas, J. F., Shea, J. G. and Sullivan, P. D.: GP 14: 75, 1956.

5 "Thus far, there has been very little evidence of actual habituation to meprobamate ['Miltown']. No real tolerance has been observed."

Borrus, J. C.: Med. Clinics of North America. In press, 1957.

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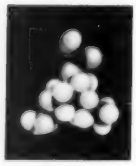

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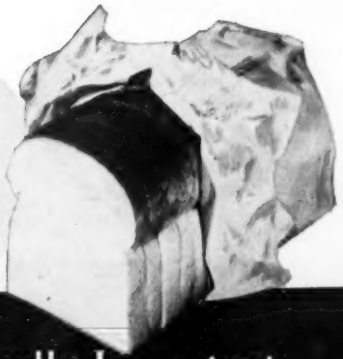

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1. Smithy, G.B., and Homburger, F.: 'Compazine' for the Treatment of Nausea and Vomiting in Patients with Advanced Cancer and Other Chronic Diseases, New England J. Med. *256*:27 (Jan. 3) 1957.

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